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(54) Title: A METHOD FOR EXTRACTING QUANTITATIVE INFORMATION RELATING TO AN INFLUENCE ON A CELLULAR RESPONSE

(57) Abstract

Cells are genetically modified to expresss a luminophore, e.g., a modified (F64L, S65T, Y66H) Green Fluorescent Protein (GFP, EGFP) coupled to a component of an intracellular signalling pathway such as a transcription factor, a cGMP- or cAMP-dependent protein kinase, a cyclin-, calmodulin- or phospholipid-dependent or mitogen-activated serine/threonin protein kinase, a tyrosine protein kinase, or a protein phosphatase (e.g. PKA, PKC, Erk, Smad, VASP, actin, p38, Jnk1, PKG, IkappaB, CDK2, Grk5, Zap70, p85, protein-tyrosine phosphatase 1C, Stat5, NFAT, NFkappaB, RhoA, PKB). An influence modulates the intracellular signalling pathway in such a way that the luminophore is being redistributed or translocated with the component in living cells in a manner experimentally determined to be correlated to the degree of the influence. Measurement of redistribution is performed by recording of light intensity, fluorescence lifetime, polarization, wavelength shift, resonance energy transfer, or other properties by an apparatus consisting of e.g. a fluorescence microscope and a CCD camera. Data stored as digital images are processed to numbers representing the degree of redistribution. The method can be used as a screening program for identifying a compound that modulates a component and is capable of treating a disease related to the function of the component.

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A METHOD for extracting quantitative information relating to an influence on a cellular response

FIELD OF INVENTION

5 The present invention relates to a method and tools for extracting quantitative information relating to an influence, on a cellular response, in particular an influence caused by contacting or incubating the cell with a substance influencing a cellular response, where the cellular response is manifested in redistribution of at least one component in the cell. In particular, the invention relates to a method for extracting quantitative information relating to an influen-10 ce on an intracellular pathway involving redistribution of at least one component associated with the pathway. The method of the invention may be used as a very efficient procedure for testing or discovering the influence of a substance on a physiological process, for example in connection with screening for new drugs, testing of substances for toxicity, identifying drug targets for known or novel drugs. Other valuable uses of the method and technology of the 15 invention will be apparent to the skilled person on the basis of the following disclosure. In a particular embodiment of the invention, the present invention relates to a method of detecting intracellular translocation or redistribution of biologically active polypeptides, preferably an enzyme, affecting intracellular processes, and a DNA construct and a cell for use in the

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method.

BACKGROUND OF THE INVENTION

Intracellular pathways are tightly regulated by a cascade of components that undergo modulation in a temporally and spatially characteristic manner. Several disease states can be attributed to altered activity of individual signalling components (i.e. protein kinases, protein phosphatases, transcription factors). These components therefore render themselves as attractive targets for therapeutic intervention.

Protein kinases and phosphatases are well described components of several intracellular signalling pathways. The catalytic activity of protein kinases and phosphatases are assumed to play a role in virtually all regulatable cellular processes. Although the involvement of protein kinases in cellular signalling and regulation have been subjected to extensive studies, detailed knowledge on e.g. the exact timing and spatial characteristics of signalling events is often difficult to obtain due to lack of a convenient technology.

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Novel ways of monitoring specific modulation of intracellular pathways in intact, living cells is assumed to provide new opportunities in drug discovery, functional genomics, toxicology, patient monitoring etc.

The spatial orchestration of protein kinase activity is likely to be essential for the high degree of specificity of individual protein kinases. The phosphorylation mediated by protein kinases is balanced by phosphatase activity. Also within the family of phosphatases translocation has been observed, e.g. translocation of PTP2C to membrane ruffles [(Cossette *et al.*1996)], and likewise is likely to be indicative of phosphatase activity.

Protein kinases often show a specific intracellular distribution before, during and after activation. Monitoring the translocation processes and/or redistribution of individual protein kinases or subunits thereof is thus likely to be indicative of their functional activity. A connection between translocation and catalytic activation has been shown for protein kinases like the diacyl glycerol (DAG)-dependent protein kinase C (PKC), the cAMP-dependent protein kinase (PKA) [(DeBernardi et al.1996)] and the mitogen-activated-protein kinase Erk-1 [(Sano et al.1995)].

Commonly used methods of detection of intracellular localisation/activity of protein kinases and phosphatases are immunoprecipitation, Western blotting and immunocytochemical detection.

Taking the family of diacyl glycerol (DAG)-dependent protein kinase Cs (PKCs) as an example, it has been shown that individual PKC isoforms that are distributed among different tissues and cells have different activator requirements and undergo differential translocation in response to activation. Catalytically inactive DAG-dependent PKCs are generally distributed throughout the cytoplasm, whereas they upon activation translocate to become associated with different cellular components, e.g. plasma membrane [(Farese, 1992),(Fulop Jr. et al. 1995)] nucleus [(Khalii et al. 1992)], cytoskeleton [(Blobe et al. 1996)]. The translocation phenomenon being indicative of PKC activation has been monitored using different approaches: a) immunocytochemistry where the localisation of individual isoforms can be detected after permeabilisation and fixation of the cells [(Khalii et al. 1992)]; and b) tagging all DAG-dependent PKC isoforms with a fluorescently labelled phorbol myristate acetate (PMA) [(Godson et al. 1996)]; and c) chemical tagging PKC b1 with the fluorophore Cy3 [(Bastiaens & Jovin 1996)] and d) genetic tagging of PKC α ([Schmidt et al. 1997]) and of PKC γ and PKC α ([Sakai et al. 1996]). The first method does not provide dynamic information whereas the latter methods will. Tagging PKC with fluorescently labelled phorbol myristate acetate cannot

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distinguish between different DAG-dependent isoforms of PKC but will label and show movement of all isoforms. Chemical and genetic labelling of specific DAG-dependent PKCs confirmed that they in an isoform specific manner upon activation move to cell periphery or nucleus.

In an alternative method, protein kinase A activity has been measured in living cells by chemical labelling one of the kinase's subunit (Adams *et al.*1991). The basis of the methodology is that the regulatory and catalytic subunit of purified protein kinase A is labelled with fluorescein and rhodamine, respectively. At low cAMP levels protein kinase A is assembled in a heterotetrameric form which enables fluorescence resonance energy transfer between the two fluorescent dyes. Activation of protein kinase A leads to dissociation of the complex, thereby eliminating the energy transfer. A disadvantage of this technology is that the labelled protein kinase A has to be microinjected into the cells of interest. This highly invasive technique is cumbersome and not applicable to large scale screening of biologically active substances. A further disadvantage of this technique as compared to the presented invention is that the labelled protein kinase A cannot be inserted into organisms/animals as a transgene.

Recently it was discovered that Green Fluorescent Protein (GFP) expressed in many different cell types, including mammalian cells, became highly fluorescent [(Chalfie et al. 1994)]. WO95/07463 describes a cell capable of expressing GFP and a method for detecting a protein of interest in a cell based on introducing into a cell a DNA molecule having DNA sequence encoding the protein of interest linked to DNA sequence encoding a GFP such that the protein produced by the DNA molecule will have the protein of interest fused to the GFP, then culturing the cells in conditions permitting expression of the fused protein and detecting the location of the fluorescence in the cell, thereby localizing the protein of interest in the cell. However, examples of such fused proteins are not provided, and the use of fusion proteins with GFP for detection or quantitation of translocation or redistribution of biologically active polypeptides affecting intracellular processes upon activation, such as proteins involved in signalling pathways, e.g. protein kinases or phosphatases, has not been suggested. WO 95/07463 further describes cells useful for the detection of molecules, such as hormones or heavy metals, in a biological sample, by operatively linking a regulatory element of the gene which is affected by the molecule of interest to a GFP, the presence of the molecules will affect the regulatory element which in turn will affect the expression of the GFP. In this way the gene encoding GFP is used as a reporter gene in a cell which is con-

structed for monitoring the presence of a specific molecular identity.

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Green Fluorescent Protein has been used in an assay for the detection of translocation of the glucocorticoid receptor (GR) [Carey, KL et al., The Journal of Cell Biology, Vol. 133, No. 5, p. 985-996 (1996)]. A GR-S65TGFP fusion has been used to study the mechanisms involved in translocation of the glucocorticoid receptor (GR) in response to the agonist dexamethasone from the cytosol, where it is present in the absence of a ligand, through the nuclear pore to the nucleus where it remains after ligand binding. The use of a GR-GFP fusion enables real-time imaging and quantitation of nuclear/cytoplasmic ratios of the fluorescence signal.

Many currently used screening programmes designed to find compounds that affect protein kinase activity are based on measurements of kinase phosphorylation of artificial or natural substrates, receptor binding and/or reporter gene expression.

DISCLOSURE OF THE INVENTION

The present invention provides an important new dimension in the investigation of cellular systems involving redistribution in that the invention provides quantification of the redistribution responses or events caused by an influence, typically contact with a chemical substance or mixture of chemical substances, but also changes in the physical environment. The quantification makes it possible to set up meaningful relationships, expressed numerically, or as curves or graphs, between the influences (or the degree of influences) on cellular systems and the redistribution response. This is highly advantageous because, as has been found, the quantification can be achieved in both a fast and reproducible manner, and - what is perhaps even more important - the systems which become quantifiable utilizing the method of the invention are systems from which enormous amounts of new information and insight can be derived.

The present screening assays have the distinct advantage over other screening assays, e.g., receptor binding assays, enzymatic assays, and reporter gene assays, in providing a system in which biologically active substances with completely novel modes of action, e.g. inhibition or promotion of redistribution/translocation of a biologically active polypeptide as a way of regulating its action rather than inhibition/activation of enzymatic activity, can be identified in a way that insures very high selectivity to the particular isoform of the biologically active polypeptide and further development of compound selectivity versus other isoforms of

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the same biologically active polypeptide or other components of the same signalling pathway.

In its broadest aspect, the invention relates to a method for extracting quantitative information relating to an influence on a cellular response, the method comprising recording variation, caused by the influence on a mechanically intact living cell or mechanically intact living cells, in spatially distributed light emitted from a luminophore, the luminophore being present in the cell or cells and being capable of being redistributed in a manner which is related with the degree of the influence, and/or of being modulated by a component which is capable of being redistributed in a manner which is related to the degree of the influence, the association resulting in a modulation of the luminescence characteristics of the luminophore, detecting and recording the spatially distributed light from the luminophore, and processing the recorded variation in the spatially distributed light to provide quantitative information correlating the spatial distribution or change in the spatial distribution to the degree of the influence. In a preferred embodiment of the invention the luminophore, which is present in the cell or cells, is capable of being redistributed by modulation of an intracellular pathway, in a manner which is related to the redistribution of at least one component of the intracellular pathway. In another preferred embodiment of the invention, the luminophore is a fluorophore.

The cells

In the invention the cell and/or cells are mechanically intact and alive throughout the experiment. In another embodiment of the invention, the cell or cells is/are fixed at a point in time after the application of the influence at which the response has been predetermined to be significant, and the recording is made at an arbitrary later time.

The mechanically intact living cell or cells could be selected from the group consisting of fungal cell or cells, such as a yeast cell or cells; invertebrate cell or cells including insect cell or cells; and vertebrate cell or cells, such as mammalian cell or cells. This cell or these cells is/are incubated at a temperature of 30°C or above, preferably at a temperature of from 32°C to 39°C, more preferably at a temperature of from 35°C to 38°C, and most preferably at a temperature of about 37°C during the time period over which the influence is observed. In one aspect of the invention the mechanically intact living cell is part of a matrix of identical or non-identical cells.

A cell used in the present invention should contain a nucleic acid construct encoding a fusion polypeptide as defined herein and be capable of expressing the sequence encoded by the construct. The cell is a eukaryotic cell selected from the group consisting of fungal cells, such as yeast cells; invertebrate cells including insect cells; vertebrate cells such as mammalian cells. The preferred cells are mammalian cells.

In another aspect of the invention the cells could be from an organism carrying in at least one of its component cells a nucleic acid sequence encoding a fusion polypeptide as defined herein and be capable of expressing said nucleic acid sequence. The organism is selected from the group consisting of unicellular and multicellular organisms, such as a mammal.

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The luminophore

The luminophore is the component which allows the redistribution to be visualised and/or recorded by emitting light in a spatial distribution related to the degree of influence. In one embodiment of the invention, the luminophore is capable of being redistributed in a manner which is physiologically relevant to the degree of the influence. In another embodiment, the luminophore is capable of associating with a component which is capable of being redistributed in a manner which is physiologically relevant to the degree of the influence. In another embodiment, the luminophore correlation between the redistribution of the luminophore and the degree of the influence could be determined experimentally. In a preferred aspect of the invention, the luminophore is capable of being redistributed in substantially the same manner as the at least one component of an intracellular pathway. In yet another embodiment of the invention, the luminophore is capable of being quenched upon spatial association with a component which is redistributed by modulation of the pathway, the quenching being measured as a change in the intensity of the luminescence.

The luminophore could be a fluorophore. In a preferred embodiment of the invention, the luminophore could be a polypeptide encoded by and expressed from a nucleotide sequence harboured in the cell or cells. The luminophore could be a hybrid polypeptide comprising a fusion of at least a portion of each of two polypeptides one of which comprises a luminescent polypeptide and the other one of which comprises a biologically active polypeptide, as defined herein.

The luminescent polypeptide could be a GFP as defined herein or could be selected from the group consisting of green fluorescent proteins having the F64L mutation as defined herein

such as F64L-GFP, F64L-Y66H-GFP, F64L-S65T-GFP, and EGFP. The GFP could be N- or C-terminally tagged, optionally via a peptide linker, to the biologically active polypeptide or a part or a subunit thereof. The fluorescent probe could be a component of a intracellular signalling pathway. The probe is coded for by a nucleic acid construct.

The pathway of investigation in the present invention could be an intracellular signalling pathway.

The influence

In a preferred embodiment of the invention, the influence could be contact between the mechanically intact living cell or the group of mechanically intact living cells with a chemical substance and/or incubation of the mechanically intact living cell or the group of mechanically intact living cells with a chemical substance. The influence will modulate the intracellular processes. In one aspect the modulation could be an activation of the intracellular processes. In another aspect the modulation could be an deactivation of the intracellular processes. In yet another aspect, the influence could inhibit or promote the redistribution without directly affecting the metabolic activity of the component of the intracellular processes.

In one embodiment the invention is used as a basis for a screening program, where the effect of unknown influences such as a compound library, can be compared to influence of known reference compounds under standardised conditions.

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The recording

In addition to the intensity, there are several parameters of fluorescence or luminescence which can be modulated by the effect of the influence on the underlying cellular phenomena, and can therefore be used in the invention. Some examples are resonance energy transfer, fluorescence lifetime, polarisation, wavelength shift. Each of these methods requires a particular kind of filter in the emission light path to select the component of the light desired and reject other components. The recording of property of light could be in the form of an ordered array of values such as a CCD array or a vacuum tube device such as a vidicon tube.

In one embodiment of the invention, the spatially distributed light emitted by a luminophore could be detected by a change in the resonance energy transfer between the luminophore and another luminescent entity capable of delivering energy to the luminophore, each of

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which has been selected or engineered to become part of, bound to or associated with particular components of the intracellular pathway. In this embodiment, either the luminophore or the luminescent entity capable of delivering energy to the luminophore undergoes redistribution in response to an influence. The resonance energy transfer would be measured as a change in the intensity of emission from the luminophore, preferably sensed by a single channel photodetector which responds only to the average intensity of the luminophore in a non-spatially resolved fashion.

In one embodiment of the invention, the recording of the spatially distributed light could be made at a single point in time after the application of the influence. In another embodiment, the recording could be made at two points in time, one point being before, and the other point being after the application of the influence. The result or variation is determined from the change in fluorescence compared to the fluorescence measured prior to the influence or modulation. In another embodiment of the invention, the recording could be performed at a series of points in time, in which the application of the influence occurs at some time after the first time point in the series of recordings, the recording being performed, e.g., with a predetermined time spacing of from 0.1 seconds to 1 hour, preferably from 1 to 60 seconds, more preferably from 1 to 30 seconds, in particular from 1 to 10 seconds, over a time span of from 1 second to 12 hours, such as from 10 seconds to 12 hours, e.g., from 10 seconds to one hour, such as from 60 seconds to 30 minutes or 20 minutes. The result or variation could also be determined from the change in fluorescence over time. The result or variation could also be determined as a change in the spatial distribution of the fluorescence over time.

Apparatus

The recording of spatially distributed luminescence emitted from the luminophore is performed by an apparatus for measuring the distribution of fluorescence in the cell or cells, and thereby any change in the distribution of fluorescence in the cell or cells, which includes at a minimum the following component parts: (a) a light source, (b) a method for selecting the wavelength(s) of light from the source which will excite the fluorescence of the protein, (c) a device which can rapidly block or pass the excitation light into the rest of the system, (d) a series of optical elements for conveying the excitation light to the specimen, collecting the emitted fluorescence in a spatially resolved fashion, and forming an image from this fluorescence emission, (e) a bench or stand which holds the container of the cells being measured in a predetermined geometry with respect to the series of optical elements, (f) a detector to

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record the spatially resolved fluorescence in the form of an image, (g) a computer or electronic system and associated software to acquire and store the recorded images, and to compute the degree of redistribution from the recorded images.

In a preferred embodiment of the invention the apparatus system is automated. In one embodiment the components in d and e mentioned above comprise a fluorescence microscope. In one embodiment the component in f mentioned above is a CCD camera.

In one embodiment the image is formed and recorded by an optical scanning system.

In one embodiment a liquid addition system is used to add a known or unknown compound to any or all of the cells in the cell holder at a time determined in advance. Preferably, the liquid addition system is under the control of the computer or electronic system. Such an automated system can be used for a screening program due to its ability to generate results from a larger number of test compounds than a human operator could generate using the apparatus in a manual fashion.

15 Quantitation of the influence

The recording of the variation or result with respect to light emitted from the luminophore is performed by recording the spatially distributed light as one or more digital images, and the processing of the recorded variation to reduce it to one or more numbers representative of the degree of redistribution comprises a digital image processing procedure or combination of digital image processing procedures. The quantitative information which is indicative of the degree of the cellular response to the influence or the result of the influence on the intracellular pathway is extracted from the recording or recordings according to a predetermined calibration based on responses or results, recorded in the same manner, to known degrees of a relevant specific influence. This calibration procedure is developed according to principles described below (Developing an Image-based Assay Technique). Specific descriptions of the procedures for particular assays are given in the examples.

While the stepwise procedure necessary to reduce the image or images to the value representative of the is particular to each assay, the individual steps are generally well-known methods of image processing. Some examples of the individual steps are point operations such as subtraction, ratioing, and thresholding, digital filtering methods such as smoothing, sharpening, and edge detection, spatial frequency methods such as Fourier filtering, image cross-correlation and image autocorrelation, object finding and classification (blob analysis),

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and colour space manipulations for visualisation. In addition to the algorithmic procedures, heuristic methods such as neural networks may also be used.

Nucleic acid constructs

- The nucleic acid constructs used in the present invention encode in their nucleic acid sequences fusion polypeptides comprising a biologically active polypeptide that is a component of an intracellular signalling pathway, or a part thereof, and a GFP, preferably an F64L mutant of GFP, N- or C-terminally fused, optionally via a peptide linker, to the biologically active polypeptide or part thereof.
- In one embodiment the biologically active polypeptide encoded by the nucleic acid construct is a protein kinase or a phosphatase.
 - In one embodiment the biologically active polypeptide encoded by the nucleic acid construct is a transcription factor or a part thereof which changes cellular localisation upon activation.
 - In one embodiment the biologically active polypeptide encoded by the nucleic acid construct is a protein, or a part thereof, which is associated with the cytoskeletal network and which changes cellular localisation upon activation.
 - In one embodiment the biologically active polypeptide encoded by the nucleic acid construct is a protein kinase or a part thereof which changes cellular localisation upon activation.
- In one embodiment the biologically active polypeptide encoded by the nucleic acid construct is a serine/threonine protein kinase or a part thereof capable of changing intracellular localisation upon activation.
 - In one embodiment the biologically active polypeptide encoded by the nucleic acid construct is a tyrosine protein kinase or a part thereof capable of changing intracellular localisation upon activation.
- In one embodiment the biologically active polypeptide encoded by the nucleic acid construct is a phospholipid-dependent serine/threonine protein kinase or a part thereof capable of changing intracellular localisation upon activation.
 - In one embodiment the biologically active polypeptide encoded by the nucleic acid construct is a cAMP-dependent protein kinase or a part thereof capable of changing cellular localisation upon activation. In a preferred embodiment the biologically active polypeptide encoded by the nucleic acid construct is a PKAc-F64L-S65T-GFP fusion.

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In one embodiment the biologically active polypeptide encoded by the nucleic acid construct is a cGMP-dependent protein kinase or a part thereof capable of changing cellular localisation upon activation.

In one embodiment the biologically active polypeptide encoded by the nucleic acid construct is a calmodulin-dependent serine/threonine protein kinase or a part thereof capable of changing cellular localisation upon activation.

In one embodiment the biologically active polypeptide encoded by the nucleic acid construct is a mitogen-activated serine/threonine protein kinase or a part thereof capable of changing cellular localisation upon activation. In preferred embodiments the biologically active polypeptide encoded by the nucleic acid constructs are an ERK1-F64L-S65T-GFP fusion or an EGFP-ERK1 fusion.

In one embodiment the biologically active polypeptide encoded by the nucleic acid construct is a cyclin-dependent serine/threonine protein kinase or a part thereof capable of changing cellular localisation upon activation.

In one embodiment the biologically active polypeptide encoded by the nucleic acid construct is a protein phosphatase or a part thereof capable of changing cellular localisation upon activation.

In one preferred embodiment of the invention the nucleic acid constructs may be DNA constructs.

- In one embodiment the biologically active polypeptide encoded by the nucleic acid construct In one embodiment the gene encoding GFP in the nucleic acid construct is derived from Aequorea victoria. In a preferred embodiment the gene encoding GFP in the nucleic acid construct is EGFP or a GFP variant selected from F64L-GFP, F64L-Y66H-GFP and F64L-S65T-GFP.
- In preferred embodiments of the invention the DNA constructs which can be identified by any of the DNA sequences shown in SEQ ID NO: 38, 40, 42, 44, 46, 48, 50, 52, 54, 56, 58, 60, 62, 64, 66, 68, 70, 72, 74, 76, 78, 108, 110, 112, 114, 116, 118, 120, 122, 124, 126, 128, 130, 132, 134, 136, 138, 140, 142 or are variants of these sequences capable of encoding the same fusion polypeptide or a fusion polypeptide which is biologically equivalent thereto, e.g. an isoform, or a splice variant or a homologue from another species.

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Screening program

The present invention describes a method that may be used to establish a screening program for the identification of biologically active substances that directly or indirectly affects intracellular signalling pathways and because of this property are potentially useful as medicaments. Based on measurements in living cells of the redistribution of spatially resolved luminescence from luminophores which undergo a change in distribution upon activation or deactivation of an intracellular signalling pathway the result of the individual measurement of each substance being screened indicates its potential biological activity.

In one embodiment of the invention the screening program is used for the identification of a biologically toxic substance as defined herein that exerts its toxic effect by interfering with an intracellular signalling pathway. Based on measurements in living cells of the redistribution of spatially resolved luminescence from luminophores which undergo a change in distribution upon activation or deactivation of an intracellular signalling pathway the result of the individual measurement of each substance being screened indicates its potential biologically toxic activity. In one embodiment of a screening program a compound that modulates a component of an intracellular pathway as defined herein, can be found and the therapeutic amount of the compound estimated by a method according to the method of the invention. In a preferred embodiment the present invention leads to the discovery of a new way of treating a condition or disease related to the intracellular function of a biologically active polypeptide comprising administration to a patient suffering from said condition or disease of an effective amount of a compound which has been discovered by any method according to the invention. In another preferred embodiment of the invention a method is established for identification of a new drug target or several new drug targets among the group of biologically active polypeptides which are components of intracellular signalling pathways.

In another embodiment of the invention an individual treatment regimen is established for the selective treatment of a selected patient suffering from an ailment where the available medicaments used for treatment of the ailment are tested on a relevant primary cell or cells obtained from said patient from one or several tissues, using a method comprising transfecting the cell or cells with at least one DNA sequence encoding a fluorescent probe according to the invention, transferring the transfected cell or cells back the said patient, or culturing the cell or cells under conditions permitting the expression of said probes and exposing it to an array of the available medicaments, then comparing changes in fluorescence patterns or redistribution patterns of the fluorescent probes in the intact living cell or cells to

detect the cellular response to the specific medicaments (obtaining a cellular action profile), then selecting one or more medicament or medicaments based on the desired activity and acceptable level of side effects and administering an effective amount of these medicaments to the selected patient.

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Back-tracking of a signal transduction pathway

The present invention describes a method that may be used to establish a screening program for back-tracking signal transduction pathways as defined herein. In one embodiment the screening program is used to establish more precisely at which level one or several compounds affect a specific signal transduction pathway by successively or in parallel testing the influence of the compound or compounds on the redistribution of spatially resolved luminescence from several of the luminophores which undergo a change in distribution upon activation or deactivation of the intracellular signalling pathway under study.

15 Construction and testing of probes

In general, a probe, i.e. a "GeneX"-GFP fusion or a GFP-"GeneX" fusion, is constructed using PCR with "GeneX"-specific primers followed by a cloning step to fuse "GeneX" in frame with GFP. The fusion may contain a short vector derived sequence between "GeneX" and GFP (e.g. part of a multiple cloning site region in the plasmid) resulting in a peptide linker between "GeneX" and GFP in the resulting fusion protein.

Detailed stepwise procedure:

- Identifying the sequence of the gene. This is most readily done by searching a depository of genetic information, e.g. the GenBank Sequence Database, which is widely available and routinely used by molecular biologists. In the specific examples below the GenBank Accession number of the gene in question is provided.
- Design of gene-specific primers. Inspection of the sequence of the gene allows design of gene-specific primers to be used in a PCR reaction. Typically, the top-strand primer encompasses the ATG start codon of the gene and the following ca. 20 nucleotides, while the bottom-strand primer encompasses the stop codon and the ca. 20 preceding nucleotides, if

the gene is to be fused behind GFP, i.e. a GFP-"GeneX" fusion. If the gene is to be fused in front of GFP, i.e. a "GeneX"-GFP fusion, a stop codon must be avoided. Optionally, the full length sequence of GeneX may not be used in the fusion, but merely the part which localizes and redistributes like GeneX in response to a signal.

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In addition to gene-specific sequences, the primers contain at least one recognition sequence for a restriction enzyme, to allow subsequent cloning of the PCR product. The sites are chosen so that they are unique in the PCR product and compatible with sites in the cloning vector. Furthermore, it may be necessary to include an exact number of nucleotides between the restriction enzyme site and the gene-specific sequence in order to establish the correct reading frame of the fusion gene and/or a translation initiation consensus sequence. Lastly, the primers always contain a few nucleotides in front of the restriction enzyme site to allow efficient digestion with the enzyme.

- -Identifying a source of the gene to be amplified. In order for a PCR reaction to produce a product with gene-specific primers, the gene-sequence must initially be present in the reaction, e.g. in the form of cDNA. Information in GenBank or the scientific literature will usually indicate in which tissue(s) the gene is expressed, and cDNA libraries from a great variety of tissues or cell types from various species are commercially available, e.g. from Clontech
 (Palo Alto), Stratagene (La Jolla) and Invitrogen (San Diego). Many genes are also available in cloned form from The American Type Tissue Collection (Virginia).
 - Optimizing the PCR reaction. Several factors are known to influence the efficiency and specificity of a PCR reaction, including the annealing temperature of the primers, the concentration of ions, notably Mg²+ and K⁺, present in the reaction, as well as pH of the reaction. If the result of a PCR reaction is deemed unsatisfactory, it might be because the parameters mentioned above are not optimal. Various annealing temperatures should be tested, e.g. in a PCR machine with a built-in temperature gradient, available from e.g. Stratagene (La Jolla), and/or various buffer compositions should be tried, e.g. the OptiPrime buffer system from Stratagene (La Jolla).

- Cloning the PCR product. The vector into which the amplified gene product will be cloned and fused with GFP will already have been taken into consideration when the primers were designed. When choosing a vector, one should at least consider in which cell types the probe subsequently will be expressed, so that the promoter controlling expression of the probe is compatible with the cells. Most expression vectors also contain one or more selective markers, e.g. conferring resistance to a drug, which is a useful feature when one wants to make stable transfectants. The selective marker should also be compatible with the cells to be used.

The actual cloning of the PCR product should present no difficulty as it typically will be a one-step cloning of a fragment digested with two different restriction enzymes into a vector digested with the same two enzymes. If the cloning proves to be problematic, it may be because the restriction enzymes did not work well with the PCR fragment. In this case one could add longer extensions to the end of the primers to overcome a possible difficulty of digestion close to a fragment end, or one could introduce an intermediate cloning step not based on restriction enzyme digestion. Several companies offer systems for this approach, e.g. Invitrogen (San Diego) and Clontech (Palo Alto).

Once the gene has been cloned and, in the process, fused with the GFP gene, the resulting product, usually a plasmid, should be carefully checked to make sure it is as expected. The most exact test would be to obtain the nucleotide sequence of the fusion-gene.

Testing the probe

Once a DNA construct for a probe has been generated, its functionality and usefulness may be tested by subjecting it to the following tests:

- Transfecting it into cells capable of expressing the probe. The fluorescence of the cell is inspected soon after, typically the next day. At this point, two features of cellular fluorescence are noted: the intensity and the sub-cellular localization.

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The intensity should usually be at least as strong as that of unfused GFP in the cells. If it is not, the sequence or quality of the probe-DNA might be faulty, and should be carefully checked.

The sub-cellular localization is an indication of whether the probe is likely to perform well. If it localizes as expected for the gene in question, e.g. is excluded from the nucleus, it can immediately go on to a functional test. If the probe is not localized soon after the transfection procedure, it may be because of overexpression at this point in time, as the cell typically will have taken of very many copies of the plasmid, and localization will occur in time, e.g. within a few weeks, as plasmid copy number and expression level decreases. If localization does not occur after prolonged time, it may be because the fusion to GFP has destroyed a localization function, e.g. masked a protein sequence essential for interaction with its normal cellular anchor-protein. In this case the opposite fusion might work, e.g. if GeneX-GFP does not work, GFP-GeneX might, as two different parts of GeneX will be affected by the proximity to GFP. If this does not work, the proximity of GFP at either end might be a problem, and it could be attempted to increase the distance by incorporating a longer linker between GeneX and GFP in the DNA construct.

If there is no prior knowledge of localization, and no localization is observed, it may be because the probe should not be localized at this point, because such is the nature of the protein fused to GFP. It should then be subjected to a functional test.

In a functional test, the cells expressing the probe are treated with at least one compound known to perturb, usually by activating, the signalling pathway on which the probe is expected to report by redistributing itself within the cell. If the redistribution is as expected, e.g. if prior knowledge tell that it should translocate from location X to location Y, it has passed the first critical test. In this case it can go on to further characterization and quantification of the response.

If it does not perform as expected, it may be because the cell lacks at least one component of the signalling pathway, e.g. a cell surface receptor, or there is species incompatibility, e.g. if the probe is modelled on sequence information of a human geneproduct, and the cell is of hamster origin. In both instances one should identify other cell types for the testing process where these potential problems would not apply.

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If there is no prior knowledge about the pattern of redistribution, the analysis of the redistribution will have to be done in greater depth to identify what the essential and indicative features are, and when this is clear, it can go on to further characterization and quantification of the response. If no feature of redistribution can be identified, the problem might be as mentioned above, and the probe should be retested under more optimal cellular conditions.

If the probe does not perform under optimal cellular conditions it's back to the drawing board.

Developing an image-based assay technique

The process of developing an image-based redistribution assay begins with either the unplanned experimental observation that a redistribution phenomenon can be visualised, or the design of a probe specifically to follow a redistribution phenomenon already known to occur. In either event, the first and best exploratory technique is for a trained scientist or technician to observe the phenomenon. Even with the rapid advances in computing technology, the human eye-brain combination is still the most powerful pattern recognition system known, and requires no advance knowledge of the system in order to detect potentially interesting and useful patterns in raw data. This is especially if those data are presented in the form of images, which are the natural "data type" for human visual processing. Because human visual processing operates most effectively in a relatively narrow frequency range, i.e., we cannot see either very fast or very slow changes in our visual field, it may be necessary to record the data and play it back with either time dilation or time compression.

Some luminescence phenomena cannot be seen directly by the human eye. Examples include polarization and fluorescence lifetime. However, with suitable filters or detectors, these signals can be recorded as images or sequences of images and displayed to the human in the fashion just described. In this way, patterns can be detected and the same methods can be applied.

Once the redistribition has been determined to be a reproducible phenomenon, one or more data sets are generated for the purpose of developing a procedure for extracting the quantitative information from the data. In parallel, the biological and optical conditions are determined which will give the best quality raw data for the assay. This can become an iterative process; it may be necessary to develop a quantitative procedure in order to assess the effect on the assay of manipulating the assay conditions.

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The data sets are examined by a person or persons with knowledge of the biological phenomenon and skill in the application of image processing techniques. The goal of this exercise is to determine or at least propose a method which will reduce the image or sequence of images constituting the record of a "response" to a value corresponding to the degree of the response. Using either interactive image processing software or an image processing toolbox and a programming language, the method is encoded as a procedure or algorithm which takes the image or images as input and generates the degree of response (in any units) as its output. Some of the criteria for evaluating the validity of a particular procedure are:

- Does the degree of the response vary in a biologically significant fashion, i.e., does it show the known or putative dependence on the concentration of the stimulating agent or condition?
- Is the degree of response reproducible, i.e., does the same concentration or level of stimulating agent or condition give the same response with an acceptable variance?
- Is the dynamic range of the response sufficient for the purpose of the assay? If not, can a change in the procedure or one of its parameters improve the dynamic range?
- Does the procedure exhibit any clear "pathologies", i.e., does it give ridiculous values for the response if there are commonly occurring imperfections in the imaging process? Can these pathologies be eliminated, controlled, or accounted for?
- Can the procedure deal with the normal variation in the number and/or size of cells in an image?

In some cases the method may be obvious; in others, a number of possible procedures may suggest themselves. Even if one method appears clearly superior to others, optimisation of parameters may be required. The various procedures are applied to the data set and the criteria suggested above are determined, or the single procedure is applied repeatedly with adjustment of the parameter or parameters until the most satisfactory combination of signal, noise, range, etc. are arrived at. This is equivalent to the calibration of any type of single-channel sensor.

The number of ways of extracting a single value from an image are extremely large, and thus an intelligent approach must be taken to the initial step of reducing this number to a small, finite number of possible procedures. This is not to say that the procedure arrived at is

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necessarily the best procedure - but a global search for the best procedure is simply out of the question due to the sheer number of possibilities involved.

Image-based assays are no different than other assay techniques in that their usefulness is characterised by parameters such as the specificity for the desired component of the sample, the dynamic range, the variance, the sensitivity, the concentration range over which the assay will work, and other such parameters. While it is not necessary to characterise each and every one of these before using the assay, they represent the only way to compare one assay with another.

10 Example: Developing a Quantitative assay for GLUT4 Translocation

GLUT4 is a member of the class of glucose transporter molecules which are important in cellular glucose uptake. It is known to translocate to the plasma membrane under some conditions of stimulation of glucose uptake. The ability to visualize the glucose uptake response noninvasively, without actually measuring glucose uptake, would be a very useful assay for anyone looking for, for example, treatments for type II diabetes.

A CHO cell line which stably expressed the human insulin receptor was used as the basis for a new cell line which stably expressed a fusion between GLUT4 and GFP. This cell line was expected to show translocation of GLUT4 to the plasma membrane as visualized by the movement of the GFP. The translocation could definitely be seen in the form of the appearance of local increases in the fluorescence in regions of the plasma membrane which had a characteristic shape or pattern. This is shown in Figure 12.

These objects became known as "snircles", and the phenomenon of their appearance as "snircling". In order to quantitate their appearance, a method had to be found to isolate them as objects in the image field, and then enumerate them, measure their area, or determine some parameter about them which correlated in a dose-dependent fashion with the concentration of insulin to which the cells had been exposed. In order to separate the snircles, a binarization procedure was applied in which one copy of the image smoothed with a relatively severe gaussian kernel (sigma = 2.5) was subtracted from another copy to which only a relatively light gaussian smooth had been applied (sigma=0.5). The resultant image was rescaled to its min/max range, and an automatic threshold was applied to divide the image into two levels. The thresholded image contains a background of one value all found object with another value. The found objects were first filtered through a filter to remove objects far too

large and far too small to be snircles. The remaining objects, which represent snircles and other artifacts from the image with approximately the same size and intensity characteristics as snircles, are passed into a classification procedure which has been previously trained with many images of snircles to recognize snircles and exclude the other artifacts. The result of this procedure is a binary image which shows only the found snircles to the degree to which the classification procedure can accurately identify them. The total area of the snircles is then summed and this value is the quantitative measure of the degree of snircling for that image.

10 Definitions:

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In the present specification and claims, the term "an influence" covers any influence to which the cellular response comprises a redistribution. Thus, e.g., heating, cooling, high pressure, low pressure, humidifying, or drying are influences on the cellular response on which the resulting redistribution can be quantified, but as mentioned above, perhaps the most important influences are the influences of contacting or incubating the cell or cells with substances which are known or suspected to exert and influence on the cellular response involving a redistribution contribution. In another embodiment of the invention the influence could be substances from a compound drug library.

In the present context, the term "green fluorescent protein" is intended to indicate a protein which, when expressed by a cell, emits fluorescence upon exposure to light of the correct excitation wavelength (cf. [(Chalfie et al.1994)]). In the following, GFP in which one or more amino acids have been substituted, inserted or deleted is most often termed "modified GFP". "GFP" as used herein includes wild-type GFP derived from the jelly fish Aequorea victoria and modifications of GFP, such as the blue fluorescent variant of GFP disclosed by Heim et al. (1994). Proc.Natl.Acad.Sci. 91:12501, and other modifications that change the spectral properties of the GFP fluorescence, or modifications that exhibit increased fluorescence when expressed in cells at a temperature above about 30°C described in PCT/DK96/00051, published as WO 97/11094 on 27 March 1997 and hereby incorporated by reference, and which comprises a fluorescent protein derived from Aequorea Green Fluorescent Protein (GFP) or any functional analogue thereof, wherein the amino acid in position 1 upstream from the chromophore has been mutated to provide an increase of fluorescence intensity when the

WO 98/45704 PCT/DK98/00145

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fluorescent protein of the invention is expressed in cells. Preferred GFP variants are F64L-GFP, F64L-Y66H-GFP and F64L-S65T-GFP. An especially preferred variant of GFP for use in all the aspects of this invention is EGFP (DNA encoding EGFP which is a F64L-S65T variant with codons optimized for expression in mammalian cells is available from Clontech, Palo Alto, plasmids containing the EGFP DNA sequence, cf. GenBank Acc. Nos. U55762, U55763).

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The term "intracellular signalling pathway" and "signal transduction pathway" are intended to indicate the coordinated intracellular processes whereby a living cell transduce an external or internal signal into cellular responses. Said signal transduction will involve an enzymatic reaction said enzymes include but are not limited to protein kinases, GTPases, ATPases, protein phosphatases, phospholipases. The cellular responses include but are not limited to gene transcription, secretion, proliferation, mechanical activity, metabolic activity, cell death.

The term "second messenger" is used to indicate a low molecular weight component invol-15 ved in the early events of intracellular signal transduction pathways.

The term "luminophore" is used to indicate a chemical substance which has the property of emitting light either inherently or upon stimulation with chemical or physical means. This includes but is not limited to fluorescence, bioluminescence, phosphorescence, chemiluminescence.

The term "mechanically intact living cell" is used to indicate a cell which is considered living according to standard criteria for that particular type of cell such as maintenance of normal membrane potential, energy metabolism, proliferative capability, and has not experienced any physically invasive treatment designed to introduce external substances into the cell such as microinjection.

The term "physiologically relevant", when applied to an experimentally determined redistribution of an intracellular component, as measured by a change in the luminescence properties or distribution, is used to indicate that said redistribution can be explained in terms of the underlying biological phenomenon which gives rise to the redistribution.

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Th terms "image processing" and "image analysis" are used to describe a large family of digital data analysis techniques or combination of such techniques which reduce ordered arrays of numbers (images) to quantitative information describing those ordered arrays of numbers. When said ordered arrays of numbers represent measured values from a physical process, the quantitative information derived is therefore a measure of the physical process.

The term "fluorescent probe" is used to indicate a fluorescent fusion polypeptide comprising a GFP or any functional part thereof which is N- or C-terminally fused to a biologically active polypeptide as defined herein, optionally via a peptide linker consisting of one or more amino acid residues, where the size of the linker peptide in itself is not critical as long as the desired functionality of the fluorescent probe is maintained. A fluorescent probe according to the invention is expressed in a cell and basically mimics the physiological behaviour of the biologically active polypeptide moiety of the fusion polypeptide.

The term "mammalian cell" is intended to indicate any living cell of mammalian origin. The cell may be an established cell line, many of which are available from The American Type Culture Collection (ATCC, Virginia, USA) or a primary cell with a limited life span derived from a mammalian tissue, including tissues derived from a transgenic animal, or a newly established immortal cell line derived froma mammalian tissue including transgenic tissues, or a hybrid cell or cell line derived by fusing different celltypes of mammalian origin e.g. hybridoma cell lines. The cells may optionally express one or more non-native gene products, e.g. receptors, enzymes, enzyme substrates, prior to or in addition to the fluorescent probe. Preferred cell lines include but are not limited to those of fibroblast origin, e.g. BHK, CHO, BALB, or of endothelial origin, e.g. HUVEC, BAE (bovine artery endothelial), CPAE (cow pulmonary artery endothelial) or of pancreatic origin, e.g. RIN, INS-1, MIN6, bTC3, aTC6, bTC6, HIT, or of hematopoietic origin, e.g. adipocyte origin, e.g. 3T3-L1, neuronal/neuroendocrine origin, e.g. AtT20, PC12, GH3, muscle origin, e.g. SKMC, A10, C2C12, renal origin, e.g. HEK 293, LLC-PK1.

The term "hybrid polypeptide" is intended to indicate a polypeptide which is a fusion of at least a portion of each of two proteins, in this case at least a portion of the green fluorescent protein, and at least a portion of a catalytic and/or regulatory domain of a protein kinase.

Furthermore a hybrid polypeptide is intended to indicate a fusion polypeptide comprising a

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GFP or at least a portion of the green fluorescent protein that contains a functional fluorophore, and at least a portion of a biologically active polypeptide as defined herein provided that said fusion is not the PKC α -GFP, PKC γ -GFP, and PKC ϵ -GFP disclosed by Schmidt et al.and Sakai et al., respectively. Thus, GFP may be N- or C-terminally tagged to a biologically active polypeptide, optionally via a linker portion or linker peptide consisting of a sequence of one or more amino acids. The hybrid polypeptide or fusion polypeptide may act as a fluorescent probe in intact living cells carrying a DNA sequence encoding the hybrid polypeptide under conditions permitting expression of said hybrid polypeptide.

The term "kinase" is intended to indicate an enzyme that is capable of phosphorylating a cellular component.

The term "protein kinase" is intended to indicate an enzyme that is capable of phosphorylating serine and/or threonine and/or tyrosine in peptides and/or proteins.

The term "phosphatase" is intended to indicate an enzyme that is capable of dephosphorylating phosphoserine and/or phosphothreonine and/or phosphotyrosine in peptides and/or proteins.

In the present context, the term "biologically active polypeptide" is intended to indicate a polypeptide affecting intracellular processes upon activation, such as an enzyme which is active in intracellular processes or a portion thereof comprising a desired amino acid sequence which has a biological function or exerts a biological effect in a cellular system. In the polypeptide one or several aminoacids may have been deleted, inserted or replaced to alter its biological function, e.g. by rendering a catalytic site inactive. Preferably, the biologically active polypeptide is selected from the group consisting of proteins taking part in an intracellular signalling pathway, such as enzymes involved in the intracellular phosphorylation and dephosphorylation processes including kinases, protein kinases and phosphorylases as defined herein, but also proteins making up the cytoskeleton play important roles in intracellular signal transduction and are therefore included in the meaning of "biologically active polypeptide" herein. More preferably, the biologically active polypeptide is a protein which according to its state as activated or non-activated changes localisation within the cell, preferably as an in-

termediary component in a signal transduction pathway. Included in this preferred group of biologically active polypeptides are cAMP dependent protein kinase A.

The term "a substance having biological activity" is intended to indicate any sample which has a biological function or exerts a biological effect in a cellular system. The sample may be a sample of a biological material such as a sample of a body fluid including blood, plasma, saliva, milk, urine, or a microbial or plant extract, an environmental sample containing pollutants including heavy metals or toxins, or it may be a sample containing a compound or mixture of compounds prepared by organic synthesis or genetic techniques.

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The phrase "any change in fluorescence" means any change in absorption properties, such as wavelength and intensity, or any change in spectral properties of the emitted light, such as a change of wavelength, fluorescence lifetime, intensity or polarisation, or any change in the intracellular localisation of the fluorophore. It may thus be localised to a specific cellular component (e.g. organelle, membrane, cytoskeleton, molecular structure) or it may be evenly distributed throughout the cell or parts of the cell.

The phrase "back-tracking of a signal transduction pathway" is intended to indicate.

The term "organism" as used herein indicates any unicellular or multicellular organism preferably originating from the animal kingdom including protozoans, but also organisms that are members of the plant kingdoms, such as algae, fungi, bryophytes, and vascular plants are included in this definition.

The term "nucleic acid" is intended to indicate any type of poly- or oligonucleic acid sequence, such as a DNA sequence, a cDNA sequence, or an RNA sequence.

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The term "biologically equivalent" as it relates to proteins is intended to mean that a first protein is equivalent to a second protein if the cellular functions of the two proteins may substitute for each other, e.g. if the two proteins are closely related isoforms encoded by different genes, if they are splicing variants, or allelic variants derived from the same gene, if they perform identical cellular functions in different cell types, or in different species. The term "biologically equivalent" as it relates to DNA is intended to mean that a first DNA sequ-

ence encoding a polypeptide is equivalent to a second DNA sequence encoding a polypeptide if the functional proteins encoded by the two genes are biologically equivalent.

The phrase "back-tracking of a signal transduction pathway" is intended to indicate a process for defining more precisely at what level a signal transduction pathway is affected, either by the influence of chemical compounds or a disease state in an organism. Consider a specific signal transduction pathway represented by the bioactive polypeptides A - B - C - D, with signal transduction from A towards D. When investigating all components of this signal transduction pathway compounds or disease states that influence the activity or redistribution of only D can be considered to act on C or downstream of C whereas compounds or disease states that influence the activity or redistribution of C and D, but not of A and B can be considered to act downstream of B.

The term "fixed cells" is used to mean cells treated with a cytological fixative such as glutaraldehyde or formaldehyde, treatments which serve to chemically cross-link and stabilize soluble and insoluble proteins within the structure of the cell. Once in this state, such proteins cannot be lost from the structure of the now-dead cell.

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BRIEF DESCRIPTION OF THE DRAWINGS

Figure 1. CHO cells expressing the PKAc-F64L-S65T-GFP hybrid protein have been treated in HAM's F12 medium with 50 mM forskolin at 37°C. The images of the GFP fluorescence in these cells have been taken at different time intervals after treatment, which were: a) 40 seconds b) 60 seconds c) 70 seconds d) 80 seconds. The fluorescence changes from a punctate to a more even distribution within the (non-nuclear) cytoplasm.

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Figure 2. Time-lapse analysis of forskolin induced PKAc-F64L-S65T-GFP redistribution. CHO cells, expressing the PKAc-F64L-S65T-GFP fusion protein were analysed by time-lapse fluorescence microscopy. Fluorescence micrographs were acquired at regular intervals from 2 min before to 8 min after the addition of agonist. The cells were challenged with 1 mM forskolin immediately after the upper left image was acquired (t=0). Frames were collected at the following times: i) 0, ii) 1, iii) 2, iv) 3, v) 4 and vi) 5 minutes. Scale bar 10 mm.

Figure 3. Time-lapse analyses of PKAc-F64L-S65T-GFP redistribution in response to various agonists. The effects of 1 mM forskolin (A), 50 mM forskolin (B), 1mM dbcAMP (C) and 100 mM IBMX (D) (additions indicated by open arrows) on the localisation of the PKAc-F64L-S65T-GFP fusion protein were analysed by time-lapse fluorescence microscopy of CHO/PKAc-F64L-S65T-GFP cells. The effect of addition of 10 mM forskolin (open arrow), followed shortly by repeated washing with buffer (solid arrow), on the localisation of the PKAc-F64L-S65T-GFP fusion protein was analysed in the same cells (E). In a parallel experiment, the effect of adding 10 mM forskolin and 100 mM IBMX (open arrow) followed by repeated washing with buffer containing 100 mM IBMX (solid arrow) was analysed (F). Removing forskolin caused PKAc-F64L-S65T-GFP fusion protein to return to the cytoplasmic aggregates while this is prevented by the continued presence of IBMX (F). The effect of 100 nM glucagon (Fig 3G, open arrow) on the localisation of the PKAc-F64L-S65T-GFP fusion protein is also shown for BHK/GR, PKAc-F64L-S65T-GFP cells. The effect of 10 mM norepinephrine (H), solid arrow, on the localisation of the PKAc-F64L-S65T-GFP fusion protein was analysed similarly, in transiently transfected CHO, PKAc-F64L-S65T-GFP cells, pretreated with 10 mM forskolin, open arrow, to increase [cAMP]. N.B. in Fig 3H the x-axis counts the image numbers, with 12 seconds between images. The raw data of each experiment consisted of 60 fluorescence micrographs acquired at regular intervals including several images acquired before the addition of buffer or agonist. The charts (A-G) each show a quantification of the response seen through all the 60 images, performed as described in analysis method 2. The change in total area of the highly fluorescent aggregates, relative to the initial area of fluorescent aggregates is plotted as the ordinate in all graphs in Figure 3, versus time for each experiment. Scale bar 10 mm.

Figure 4. Dose response curve (two experiments) for forskolin-induced redistribution of the PKAc-F64L-S65T-GFP fusion.

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Figure 5. Time from initiation of a response to half maximal ($t_{1/2max}$) and maximal (t_{max}) PKAc-F64L-S65T-GFP redistribution. The data was extracted from curves such as that shown in "Figure 2." All $t_{1/2max}$ and t_{max} values are given as mean±SD and are based on a total of 26-30 cells from 2-3 independent experiments for each forskolin concentration. Since the observed redistribution is sustained over time, the t_{max} values were taken as the earliest time point at which complete redistribution is reached. Note that the values do not relate to the degree of redistribution.

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Figure 6. Parallel dose response analyses of forskolin induced cAMP elevation and PKAc-F64L-S65T-GFP redistribution. The effects of buffer or 5 increasing concentrations of forskolin on the localisation of the PKAc-F64L-S65T-GFP fusion protein in CHO/PKAc-F64L-S65T-GFP cells, grown in a 96 well plate, were analysed as described above. Computing the ratio of the SD's of fluorescence micrographs taken of the same field of cells, prior to and 30 min after the addition of forskolin, gave a reproducible measure of PKAc-F64L-S65T-GFP redistribution. The graph shows the individual 48 measurements and a trace of their mean±s.e.m at each forskolin concentration. For comparison, the effects of buffer or 8 increasing concentrations of forskolin on [cAMP], was analysed by a scintillation proximity assay of cells grown under the same conditions. The graph shows a trace of the mean ± s.e.m of 4 experiments expressed in arbitrary units.

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Figure 7. BHK cells stably transfected with the human muscarinic (hM1) receptor and the PKCa-F64L-S65T-GFP fusion. Carbachol (100 mM added at 1.0 second) induced a transient redistribution of PKCa-F64L-S65T-GFP from the cytoplasm to the plasma membrane. Images were taken at the following times: a) 1 second before carbachol addition, b) 8.8 seconds after addition and c) 52.8 seconds after addition.

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Figure 8. BHK cells stably transfected with the hM1 receptor and PKCa-F64L-S65T-GFP fusion were treated with carbachol (1 mM, 10 mM, 100 mM). In single cells intracellular [Ca²+] was monitored simultaneously with the redistribution of PKCa-F64L-S65T-GFP. Dashed line indicates the addition times of carbachol. The top panel shows changes in the intracellular Ca²+ concentration of individual cells with time for each treatment. The middle panel shows changes in the average cytoplasmic GFP fluorescence for individual cells against time for each treatment. The bottom panel shows changes in the fluorescence of the periphery of single cells, within regions that specifically include the circumferential edge of a cell as seen in normal projection, the regions which offers best chance to monitor changes in the fluorescence intensity of the plasma membrane.

Figure 9. a) The hERK1-F64L-S65T-GFP fusion expressed in HEK293 cells treated with 100 mM of the MEK1 inhibitor PD98059 in HAM F-12 (without serum) for 30 minutes at 37 °C. The nuclei empty of fluorescence during this treatment.

- b) The same cells as in (a) following treatment with 10 % foetal calf serum for 15 minutes at 37 °C.
- c) Time profiles for the redistribution of GFP fluorescence in HEK293 cells following treatment with various concentrations of EGF in Hepes buffer (HAM F-12 replaced with Hepes buffer directly before the experiment). Redistribution of fluorescence is expressed as the change in the ratio value between areas in nucleus and cytoplasm of single cells. Each time profile is the mean for the changes seen in six single cells.
- d) Bar chart for the end-point measurements, 600 seconds after start of EGF treatments, of fluorescence change (nucleus:cytoplasm) following various concentrations of EGF.

Figure 10.

- a) The SMAD2-EGFP fusion expressed in HEK293 cells starved of serum overnight in HAM F-12. HAM F-12 was then replaced with Hepes buffer pH 7.2 immediately before the experiment. Scale bar is 10 mm.
- b) HEK 293 cells expressing the SMAD2-EGFP fusion were treated with various concentration of TGF-beta as indicated, and the redistribution of fluorescence monitored against time.

The time profile plots represent increases in fluorescence within the nucleus, normalised to starting values in each cell measured. Each trace is the time profile for a single cell nucleus.

c) A bar chart representing the end-point change in fluorescence within nuclei (after 850 seconds of treatment) for different concentrations of TGF-beta. Each bar is the value for a single nucleus in each treatment.

Figure 11. The VASP-F64L-S65T-GFP fusion in CHO cells stably transfected with the human insulin receptor. The cells were starved for two hours in HAM F-12 without serum, then treated with 10% foetal calf serum. The image shows the resulting redistribution of fluorescence after 15 minutes of treatment. GFP fluorescence becomes localised in structures identified as focal adhesions along the length of actin stress fibres.

Figure 12. Time lapse recording GLUT4-GFP redistribution in CHO-HIR cells. Time indicates minutes after the addition of 100 nM insulin.

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EXAMPLE 1

5 Construction, testing and implementation of an assay for cAMP based on PKA activation in real time within living cells.

Useful for monitoring the activity of signalling pathways which lead to altered concentrations of cAMP, e.g. activation of G-protein coupled receptors which couple to G-proteins of the G_s or G_i class.

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The catalytic subunit of the murine cAMP dependent protein kinase (PKAc)was fused C-terminally to a F64L-S65T derivative of GFP. The resulting fusion (PKAc-F64L-S65T-GFP) was used for monitoring *in vivo* the translocation and thereby the activation of PKA.

Construction of the PKAc-F64L-S65T-GFP fusion:

15 Convenient restriction endonuclease sites were introduced into the cDNAs encoding murine PKAc (Gen Bank Accession number: M12303) and F64L-S65T-GFP (sequence disclosed in WO 97/11094) by polymerase chain reaction (PCR). The PCR reactions were performed according to standard protocols with the following primers:

5'PKAc: TTggACACAAgCTTTggACACCCTCAggATATgggCAACgCCgCCgCCGCCAAg (SEQ ID NO:3),

3'PKAc: gTCATCTTCTCgAgTCTTTCAggCgCgCCCAAACTCAgTAAACTCCTTgCCACAC (SEQ ID NO:4),

5'GFP: TTggACACAAgCTTTggACACggCgCgCCATgAgTAAAggAgAACTTTTC (SEQ ID NO:1),

25 3'GFP: gTCATCTTCTCgAgTCTTACTCCTgAggTTTgTATAgTTCATCCATgCCATgT (SEQ ID NO:2).

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The PKAc amplification product was then digested with HindIII+AscI and the F64L-S65T-GFP product with AscI+XhoI. The two digested PCR products were subsequently ligated with a HindIII+XhoI digested plasmid (pZeoSV® mammalian expression vector, Invitrogen, San Diego, CA, USA). The resulting fusion construct (SEQ ID NO:68 & 69) was under control of the SV40 promoter.

Transfection and cell culture conditions.

Chinese hamster ovary cells (CHO), were transfected with the plasmid containing the PKAc-F64L-S65T-GFP fusion using the calcium phosphate precipitate method in HEPES-buffered saline (Sambrook *et al.*, 1989). Stable transfectants were selected using 1000 mg Zeocin/ml (Invitrogen) in the growth medium (DMEM with 1000 mg glucose/l, 10 % fetal bovine serum (FBS), 100 mg penicillin-streptomycin mixture ml⁻¹, 2 mM L-glutamine purchased from Life Technologies Inc., Gaithersburg, MD, USA). Untransfected CHO cells were used as the control. To assess the effect of glucagon on fusion protein translocation, the PKAc-F64L-S65T-GFP fusion was stably expressed in baby hamster kidney cells overexpressing the human glucagon receptor (BHK/GR cells) Untransfected BHK/GR cells were used as the control. Expression of GR was maintained with 500 mg G418/ml (*Neo* marker) and PKAc-F64L-S65T-GFP was maintained with 500 mg Zeocin/ml (*Sh ble* marker). CHO cells were also simultaneously co-transfected with vectors containing the PKAc-F64L-S65T-GFP fusion and the human a2a adrenoceptor (hARa2a).

For fluorescence microscopy, cells were allowed to adhere to Lab-Tek chambered coverglasses (Nalge Nunc Int., Naperville, IL, USA) for at least 24 hours and cultured to about 80% confluence. Prior to experiments, the cells were cultured over night without selection pressure in HAM F-12 medium with glutamax (Life Technologies), 100 mg penicillinstreptomycin mixture ml⁻¹ and 0.3 % FBS. This medium has low autofluorescence enabling fluorescence microscopy of cells straight from the incubator.

Monitoring activity of PKA activity in real time:

Image aquisition of live cells were gathered using a Zeiss Axiovert 135M fluorescence microscope fitted with a Fluar 40X, NA: 1.3 oil immersion objective and coupled to a Photometrics CH250 charged coupled device (CCD) camera. The cells were illuminated with a 100 W HBO arc lamp. In the light path was a 470±20 nm excitation filter, a 510 nm dichroic mirror

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and a 515±15 nm emission filter for minimal image background. The cells were kept and monitored to be at 37°C with a custom built stage heater.

Images were processed and analyzed in the following manner:.

Method 1: Stepwise procedure for quantitation of translocation of PKA:

- 1. The image was corrected for dark current by performing a pixel-by-pixel subtraction of a dark image (an image taken under the same conditions as the actual image, except the camera shutter is not allowed to open).
 - 2. The image was corrected for non-uniformity of the illumination by performing a pixel-by-pixel ratio with a flat field correction image (an image taken under the same conditions as the actual image of a uniformly fluorescent specimen).
 - 3. The image histogram, i.e., the frequency of occurrence of each intensity value in the image, was calculated.
 - 4. A smoothed, second derivative of the histogram was calculated and the second zero is determined. This zero corresponds to the inflection point of the histogram on the high side of the main peak representing the bulk of the image pixel values.
 - 5. The value determined in step 4 was subtracted from the image. All negative values were discarded.
 - 6. The variance (square of the standard deviation) of the remaining pixel values was determined. This value represents the "response" for that image.
- 20 7. Scintillation proximity assay (SPA) for independent quantitation of cAMP:

Method 2: Alternative method for quantitation of PKA redistribution:

- 1. The fluorescent aggregates are segmented from each image using an automatically found threshold based on the maximisation of the information measure between the object and background. The *a priori* entropy of the image histogram is used as the information measure.
 - 2. The area of each image occupied by the aggregates is calculated by counting pixels in the segmented areas.
- 3. The value obtained in step 2 for each image in a series, or treatment pair, is normalised to the value found for the first (unstimulated) image collected. A value of zero (0) indicates no redistribution of fluorescence from the starting condition. A value of one (1) by this method equals full redistribution.
- 15 Cells were cultured in HAM F-12 medium as described above, but in 96-well plates. The medium was exchanged with Ca²⁺-HEPES buffer including 100 mM IBMX and the cells were stimulated with different concentrations of forskolin for 10 min. Reactions were stopped with addition of NaOH to 0.14 M and the amount of cAMP produced was measured with the cAMP-SPA kit, RPA538 (Amersham) as described by the manufacturer.

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Manipulating intracellular levels of cAMP to test the PKAc-F64L-S65T-GFP fusion.

The following compounds were used to vary cAMP levels: Forskolin, an activator of adenylate cyclase; dbcAMP, a membrane permeable cAMP analog which is not degraded by phosphodiesterase; IBMX, an inhibitor of phosphodiesterase.

- CHO cells stably expressing the PKAc-F64L-S65T-GFP, showed a dramatic translocation of the fusion protein from a punctate distribution to an even distribution throughout the cytoplasm following stimulation with 1 mM forskolin (n=3), 10 mM forskolin (n=4) and 50 mM forskolin (n=4) (Fig 1), or dbcAMP at 1mM (n=6).
- Fig. 2 shows the progression of response in time following treatment with 1 mM forskolin.

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Fig. 3 gives a comparison of the average temporal profiles of fusion protein redistribution and a measure of the extent of each response to the three forskolin concentrations (Fig. 3A, E, B), and to 1 mM dbcAMP (fig 3C) which caused a similar but slower response, and to addition of 100 mM IBMX (n=4, Fig. 3D) which also caused a slow response, even in the absence of adenylate cyclase stimulation. Addition of buffer (n=2) had no effect (data not shown).

As a control for the behavior of the fusion protein, F64L-S65T-GFP alone was expressed in CHO cells and these were also given 50 mM forskolin (n=5); the uniform diffuse distribution characteristic of GFP in these cells was unaffected by such treatment (data not shown).

The forskolin induced translocation of PKAc-F64L-S65T-GFP showed a dose-response relationship (Fig 4 and 6), see quantitative procedures above.

Reversibility of PKAc-F64L-S65T-GFP translocation.

The release of the PKAc probe from its cytoplasmic anchoring hotspots was reversible. Washing the cells repeatedly (5-8 times) with buffer after 10µM forskolin treatment completely restored the punctate pattern within 2-5 min (n=2, Fig. 3E). In fact the fusion protein returned to a pattern of fluorescent cytoplasmic aggregates virtually indistinguishable from that observed before forskolin stimulation.

To test whether the return of fusion protein to the cytoplasmic aggregates reflected a decreased [cAMP], cells were treated with a combination of 10 mM forskolin and 100 mM IBMX (n=2) then washed repeatedly (5-8 times) with buffer containing 100 mM IBMX (Fig. 3F). In these experiments, the fusion protein did not return to its prestimulatory localization after removal of forskolin.

25 Testing the PKA-F64L-S65T-GFP probe with physiologically relevant agents.

To test the probe's response to receptor activation of adenylate cyclase, BHK cells stably transfected with the glucagon receptor and the PKA-F64L-S65T-GFP probe were exposed to glucagon stimulation. The glucagon receptor is coupled to a G_s protein which activates adenylate cyclase, thereby increasing the cAMP level. In these cells, addition of 100 nM glucagon (n=2) caused the release of the PKA-F64L-S65T-GFP probe from the cytoplasmic aggregates and a resulting translocation of the fusion protein to a more even cytoplasmic

distribution within 2-3 min (Fig. 3G). Similar but less pronounced effects were seen at lower glucagon concentrations (n=2, data not shown). Addition of buffer (n=2) had no effect over time (data not shown).

Transiently transfected CHO cells expressing hARa2a and the PKA-F64L-S65T-GFP probe were treated with 10 mM forskolin for 7.5 minutes, then, in the continued presence of forskolin, exposed to 10 mM norepinephrine to stimulate the exogenous adrenoreceptors, which couple to a G₁ protein, which inhibit adenylate cyclase. This treatment led to reappearance of fluorescence in the cytoplasmic aggregates indicative of a decrease in [cAMP]₁ (Fig. 3H).

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Fusion protein translocation correlated with [cAMP]_i

As described above, the time it took for a response to come to completion was dependent on the forskolin dose (Fig. 5) In addition the degree of responses was also dose dependent. To test the PKA-F64L-S65T-GFP fusion protein translocation in a semi high through-put system, CHO cells stably transfected with the PKA-F64L-S65T-GFP fusion was stimulated with buffer and 5 increasing doses of forskolin (n=8). Using the image analysis algorithm described above (Method 1), a dose response relationship was observed in the range from 0.01-50 mM forskolin (Fig. 6). A half maximal stimulation was observed at about 2 mM forskolin. In parallel, cells were stimulated with buffer and 8 increasing concentrations of forskolin (n=4) in the range 0.01-50 mM. The amount of cAMP produced was measured in an SPA assay. A steep increase was observed between 1 and 5 mM forskolin coincident with the steepest part of the curve for fusion protein translocation (also Fig. 6)

25 EXAMPLE 2

Quantitation of redistribution in real-time within living cells.

Probe for detection of PKC activity in real time within living cells:

Construction of PKC-GFP fusion:

The probe was constructed by ligating two restriction enzyme treated polymerase chain reaction (PCR) amplification products of the cDNA for murine PKCα (GenBank Accession number: M25811) and F64L-S65T-GFP (sequence disclosed in WO 97/11094) respectively. Tag® polymerase and the following oligonucleotide primers were used for PCR;

5'mPKCa: TTggACACAAgCTTTggACACCCTCAggATATggCTgACgTTTACCCggCCAACg (SEQ ID NO:5),

3'mPKCa: gTCATCTTCTCgAgTCTTTCAggCgCgCCCTACTgCACTTTgCAAgATTgggTgC (SEQ ID NO:6),

5'F64L-S65T-GFP: TTggACACAAgCTTTggACACggCgCgCCATgAgTAAAggAgAACTT-TTC (SEQ ID NO:1),

3'F64L-S65T-GFP: gTCATCTTCTCgAgTCTTACTCCTgAggTTTgTATAgTTCATCCATgC-CATgT (SEQ ID NO:2).

The hybrid DNA strand was inserted into the pZeoSV® mammalian expression vector as a HindIII-Xhol casette as described in example 1.

15 Cell Culture:

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BHK cells expressing the human M1 receptor under the control of the inducible metallothionine promoter and maintained with the dihydrofolate reductase marker were transfected with the PKC α -F64L-S65T-GFP probe using the calcium phosphate precipitate method in HEPES buffered saline (HBS [pH 7.10]). Stable transfectants were selected using 1000 μ g Zeocin®/ml in the growth medium (DMEM with 1000 mg glucose/l, 10 % foetal bovine serum (FBS), 100 mg penicillin-streptomycin mixture ml-1, 2 mM l-glutamine). The hM1 receptor and PKC α -F64L-S65T-GFP fusion protein were maintained with 500 nM methotrexate and 500 μ g Zeocin®/ml respectively. 24 hours prior to any experiment, the cells were transferred to HAM F-12 medium with glutamax, 100 μ g penicillin-streptomycin mixture ml-1 and 0.3 % FBS. This medium relieves selection pressure, gives a low induction of signal transduction pathways and has a low autofluorescence at the relevant wavelength enabling fluorescence microscopy of cells straight from the incubator.

Monitoring the PKC activity in real time:

Digital images of live cells were gathered using a Zeiss Axiovert 135M fluorescence microscope fitted with a 40X, NA: 1.3 oil immersion objective and coupled to a Photometrics

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CH250 charged coupled device (CCD) camera. The cells were illuminated with a 100 W arc lamp. In the light path was a 470±20 nm excitation filter, a 510 nm dichroic mirror and a 515±15 nm emission filter for minimal image background. The cells were kept and monitored to be at 37°C with a custom built stage heater.

5 Images were analyzed using the IPLab software package for Macintosh.

Upon stimulation of the M1-BHK cells, stably expressing the PKCα-F64L-S65T-GFP fusion, with carbachol we observed a dose-dependent transient translocation from the cytoplasm to the plasma membrane (Fig. 7a,b,c). Simultaneous measurement of the cytosolic free calcium concentration shows that the carbachol-induced calcium mobilisation precedes the translocation (Fig. 8).

Stepwise procedure for quantitation of translocation of PKC:

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- 1. The image was corrected for dark current by performing a pixel-by-pixel subtraction of a dark image (an image taken under the same conditions as the actual image, except the camera shutter is not allowed to open).
- 2. The image was corrected for non-uniformity of the illumination by performing a pixel-by-15 pixel ratio with a flat field correction image (an image taken under the same conditions as the actual image of a uniformly fluorescent specimen).
 - 3. A copy of the image was made in which the edges are identified. The edges in the image are found by a standard edge-detection procedure – convolving the image with a kernel which removes any large-scale unchanging components (i.e., background) and accentuates any small-scale changes (i.e., sharp edges). This image was then converted to a binary image by threshholding. Objects in the binary image which are too small to represent the edges of cells were discarded. A dilation of the binary image was performed to close any gaps in the Image edges. Any edge objects in the image which were in contact with the borders of the image are discarded. This binary image represents the edge mask.
 - Another copy of image was made via the procedure in step 3. This copy was further processed to detect objects which enclose "holes" and setting all pixels inside the holes to the binary value of the edge, i.e., one. This image represents the whole cell mask.
- The original image was masked with the edge mask from step 3 and the sum total of all pixel values is determined. 30

- 6. The original image was masked with the whole cell mask from step 4 and the sum total of all pixel values was determined.
- 7. The value from step 5 was divided by the value from step 6 to give the final result, the fraction of fluorescence intensity in the cells which was localized in the edges.

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EXAMPLE 3

Probes for detection of mitogen activated protein kinase Erk1 redistribution.

Useful for monitoring signalling pathways involving MAPK, e.g. to identify compounds which modulate the activity of the pathway in living cells.

Erk1, a serine/threonine protein kinase, is a component of a signalling pathway which is activated by e.g. many growth factors.

Probes for detection of ERK-1 activity in real time within living cells:

- The extracellular signal regulated kinase (ERK-1, a mitogen activated protein kinase, MAPK) is fused N- or C-terminally to a derivative of GFP. The resulting fusions expressed in different mammalian cells are used for monitoring *in vivo* the nuclear translocation, and thereby the activation, of ERK1 in response to stimuli that activate the MAPK pathway.
 - a) Construction of murine ERK1 F64L-S65T-GFP fusion:
- Convenient restriction endonuclease sites are introduced into the cDNAs encoding murine ERK1 (GenBank Accession number: Z14249) and F64L-S65T-GFP (sequence disclosed in WO 97/11094) by polymerase chain reaction (PCR). The PCR reactions are performed according to standard protocols with the following primers:

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5'F64L-S65T-GFP: TTggACACAAgCTTTggACACggCgCgCCATgAgTAAAggAgAACTT-TTC (SEQ ID NO:1)

5 3'F64L-S65T-GFP: gTCATCTTCTCgAgTCTTACTCCTgAggTTTgTATAgTTCATCCATgC-CATgT (SEQ ID NO:2)

To generate the mERK1-F64L-S65T-GFP (SEQ ID NO:56 & 57) fusion the ERK1 amplification product is digested with HindIII+AscI and the F64L-S65T-GFP product with AscI+Xhol. To generate the F64L-S65T-GFP-mERK1 fusion the ERK1 amplification product is then digested with HindIII+Bsu36I and the F64L-S65T-GFP product with Bsu36I+Xhol. The two pairs of digested PCR products are subsequently ligated with a HindIII+Xhol digested plasmid (pZeoSV® mammalian expression vector, Invitrogen, San Diego, CA, USA). The resulting fusion constructs are under control of the SV40 promoter.

b) The human Erk1 gene (GenBank Accession number: X60188) was amplified using PCR according to standard protocols with primers Erk1-top (SEQ ID NO:9) and Erk1-bottom/+stop (SEQ ID NO:10). The PCR product was digested with restriction enzymes E-coR1 and BamH1, and ligated into pEGFP-C1 (Clontech, Palo Alto; GenBank Accession number U55763) digested with EcoR1 and BamH1. This produces an EGFP-Erk1 fusion
 (SEQ ID NO:38 &39) under the control of a CMV promoter.

The plasmid containing the EGFP-Erk1 fusion was transfected into HEK293 cells employing the FUGENE transfection reagent (Boehringer Mannheim). Prior to experiments the cells were grown to 80%-90% confluency 8 well chambers in DMEM with 10% FCS. The cells were washed in plain HAM F-12 medium (without FCS), and then incubated for 30-60 minutes in plain HAM F-12 (without FCS) with 100 micromolar PD98059, an inhibitor of MEK1, a kinase which activates Erk1; this step effectively empties the nucleus of EGFP-Erk1. Just before starting the experiment, the HAM F-12 was replaced with Hepes buffer following a wash with Hepes buffer. This removes the PD98059 inhibitor; if blocking of MEK1 is still wanted (e.g. in control experiments), the inhibitor is included in the Hepes buffer.

The experimental setup of the microscope was as described in example 1.

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60 images were collected with 10 seconds between each, and with the test compound added after image number 10.

Addition of EGF (1-100 nM) caused within minutes a redistribution of EGFP-Erk1 from the cytoplasm into the nucleus (Fig. 9a,b).

The response was quantitated as described below and a dose-dependent relationship between EGF concentration and nuclear translocation of EGFP-Erk1 was found (Fig. 9c,d). Reditribution of GFP fluorescence is expressed in this example as the change in the ratio value between areas in nuclear versus cytoplasmic compartments of the cell. Each time profile is the average of nuclear to cytoplasmic ratios from six cells in each treatment.

EXAMPLE 4:

Probes for detection of Erk2 redistribution.

Useful for monitoring signalling pathways involving MAPK, e.g. to identify compounds which modulate the activity of the pathway in living cells.

Erk2, a serine/threonine protein kinase, is closely related to Erk1 but not identical; it is a component of a signalling pathway which is activated by e.g. many growth factors.

- a) The rat Erk2 gene (GenBank Accession number: M64300) was amplified using PCR according to standard protocols with primers Erk2-top (SEQ ID NO:11) and Erk2-bottom/+stop (SEQ ID NO:13) The PCR product was digested with restriction enzymes Xho1 and BamH1, and ligated into pEGFP-C1 (Clontech, Palo Alto; GenBank Accession number U55763) digested with Xho1 and BamH1. This produces an EGFP-Erk2 fusion (SEQ ID NO:40 &41) under the control of a CMV promoter.
- b) The rat Erk2 gene (GenBank Accession number: M64300) was amplified using PCR according to standard protocols with primers (SEQ ID NO:11) Erk2-top and Erk2-bottom/-stop (SEQ ID NO:12). The PCR product was digested with restriction enzymes Xho1 and BamH1, and ligated into pEGFP-N1 (Clontech, Palo Alto; GenBank Accession number U55762) digested with Xho1 and BamH1. This produces an Erk2-EGFP fusion (SEQ ID NO:58 &59) under the control of a CMV promoter.

The resulting plasmids were transfected into CHO cells and BHK cells. The cells were grown under standard conditions. Prior to experiments, the cells were starved in medium without serum for 48-72 hours. This led to a predominantly cytoplasmic localization of both probes, especially in BHK cells. 10% fetal calf serum was added to the cells and the fluorescence of the cells was recorded as explained in example 3. Addition of serum caused the probes to redistribute into the nucleus within minutes of addition of serum.

EXAMPLE 5:

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10 Probes for detection of Smad2 redistribution.

Useful for monitoring signalling pathways activated by some members of the transforming growth factor-beta family, e.g. to identify compounds which modulate the activity of the pathway in living cells.

Smad 2, a signal transducer, is a component of a signalling pathway which is induced by some members of the TGFbeta family of cytokines.

- a) The human Smad2 gene (GenBank Accession number: AF027964) was amplified using PCR according to standard protocols with primers Smad2-top (SEQ ID NO:24) and Smad2-bottom/+stop (SEQ ID NO:26). The PCR product was digested with restriction enzymes E-coR1 and Acc65I, and ligated into pEGFP-C1 (Clontech; Palo Alto; GenBank Accession number U55763) digested with EcoR1 and Acc65I. This produces an EGFP-Smad2 fusion (SEQ ID NO:50&51) under the control of a CMV promoter.
- b) The human Smad2 gene (GenBank Accession number: AF027964) was amplified using PCR according to standard protocols with primers Smad2-top (SEQ ID NO:24) and Smad2-bottom/-stop (SEQ ID NO:25). The PCR product was digested with restriction enzymes E-coR1 and Acc65I, and ligated into pEGFP-N1 (Clontech, Palo Alto; GenBank Accession number U55762) digested with EcoR1 and Acc65I. This produces a Smad2-EGFP fusion (SEQ ID NO:74 &75) under the control of a CMV promoter.
- The plasmid containing the EGFP-Smad2 fusion was transfected into HEK293 cells, where it showed a cytoplasmic distribution. Prior to experiments the cells were grown in 8 well Nunc

chambers in DMEM with 10% FCS to 80% confluency and starved overnight in HAM F-12 medium without FCS.

For experiments, the HAM F-12 medium was replaced with Hepes buffer pH 7.2.

The experimental setup of the microscope was as described in example 1.

90 images were collected with 10 seconds between each, and with the test compound added after image number 5.

After serum starvation of cells, each nucleus contains less GFP fluorescence than the surrounding cytoplasm (Fig. 10a). Addition of TGFbeta caused within minutes a redistribution of EGFP-Smad2 from the cytoplasma into the nucleus (Fig. 10b).

The redistribution of fluorescence within the treated cells was quantified simply as the fractional increase in nuclear fluorescence normalised to the starting value of GFP fluorescence in the nucleus of each unstimulated cell.

15 EXAMPLE 6:

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Probe for detection of VASP redistribution.

Useful for monitoring signalling pathways involving rearrangement of cytoskeletal elements, e.g. to identify compounds which modulate the activity of the pathway in living cells.

VASP, a phosphoprotein, is a component of cytoskeletal structures, which redistributes in response to signals which affect focal adhesions.

a) The human VASP gene (GenBank Accession number: Z46389) was amplified using PCR according to standard protocols with primers VASP-top (SEQ ID NO:94) and VASP-bottom/+stop (SEQ ID NO:95). The PCR product was digested with restriction enzymes Hind3 and BamH1, and ligated into pEGFP-C1 (Clontech, Palo Alto; GenBank Accession number U55763) digested with Hind3and BamH1. This produces an EGFP-VASP fusion (SEQ ID NO:124 &125) under the control of a CMV promoter.

The resulting plasmid was transfected into CHO cells expressing the human insulin receptor using the calcium-phosphate transfection method. Prior to experiments, cells were grown in 8 well Nunc chambers and starved overnight in medium without FCS.

Experiments are performed in a microscope setup as described in example 1.

10% FCS was added to the cells and images were collected. The EGFP-VASP fusion was redistributed from a somewhat even distribution near the periphery into more localized structures, identified as focal adhesion points (Fig. 11).

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A large number of further GFP fusions have been made or are in the process of being made, as apparent from the following Examples 7-22 which also suggest suitable host cells and substances for activation of the cellular signalling pathways to be monitored and analyzed.

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EXAMPLE 7:

Probe for detection of actin redistribution.

Useful for monitoring signalling pathways involving rearrangement or formation of actin filaments, e.g. to identify compounds which modulate the activity of pathways leading to cytoskeletal rearrangements in living cells.

Actin is a component of cytoskeletal structures, which redistributes in response to very many cellular signals.

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The actin binding domain of the human alpha-actinin gene (GenBank Accession number: X15804) was amplified using PCR according to standard protocols with primers ABD-top (SEQ ID NO:90) and ABD-bottom/-stop (SEQ ID NO:91). The PCR product was digested with restriction enzymes Hind3 and BamH1, and ligated into pEGFP-N1 (Clontech, Palo Alto; GenBank Accession number U55762) digested with Hind3 and BamH1. This produced an actin-binding-domain-EGFP fusion (SEQ ID NO:128 &129) under the control of a CMV promoter.

The resulting plasmid was transfected into CHO cells expressing the human insulin receptor. Cells were stimulated with insulin which caused the actin binding domain-EGFP probe to become redistributed into morphologically distinct membrane-associated structures.

Example 8:

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Probes for detection of p38 redistribution.

Useful for monitoring signalling pathways responding to various cellular stress situations, e.g. to identify compounds which modulate the activity of the pathway in living cells, or as a counterscreen.

p38, a serine/thronine protein kinase, is a component of a stress-induced signalling pathway which is activated by many types of cellular stress, e.g. TNFalpha, anisomycin, UV and mitomycin C.

- a) The human p38 gene (GenBank Accession number: L35253) was amplified using PCR according to standard protocols with primers p38-top (SEQ ID NO:14) and p38-bottom/+stop (SEQ ID NO: 16). The PCR product was digested with restriction enzymes Xho1 and BamH1, and ligated into pEGFP-C1 (Clontech, Palo Alto; GenBank Accession number U55763) digested with Xho1 and BamH1. This produced an EGFP-p38 fusion (SEQ ID NO:46 &47) under the control of a CMV promoter.
- b) The human p38 gene (GenBank Accession number: L35253) was amplified using PCR according to standard protocols with primers p38-top (SEQ ID NO:13) and p38-bottom/-stop (SEQ ID NO:15). The PCR product was digested with restriction enzymes Xho1 and BamH1, and ligated into pEGFP-N1 (Clontech, Palo Alto; GenBank Accession number U55762) digested with Xho1 and BamH1. This produced a p38-EGFP fusion (SEQ ID NO:64 &65) under the control of a CMV promoter.

The resulting plasmids are transfected into a suitable cell line, e.g. HEK293, in which the EGFP-p38 probe and/or the p38-EGFP probe should change its cellular distribution from predominantly cytoplasmic to nuclear within minutes in response to activation of the signal-ling pathway with e.g. anisomycin.

Example 9:

30 Probes for detection of Jnk1 redistribution.

Useful for monitoring signalling pathways responding to various cellular stress situations, e.g. to identify compounds which modulate the activity of the pathway in living cells, or as a counterscreen.

Jnk1, a serine/threonine protein kinase, is a component of a stress-induced signalling pathway different from the p38 described above, though it also is activated by many types of cellular stress, e.g. TNFalpha, anisomycin and UV.

- a) The human Jnk1 gene (GenBank Accession number: L26318) was amplified using PCR according to standard protocols with primers Jnk-top (SEQ ID NO:17) and Jnk-bottom/+stop (SEQ ID NO:19). The PCR product was digested with restriction enzymes Xho1 and BamH1, and ligated into pEGFP-C1 (Clontech, Palo Alto; GenBank Accession number U55763) digested with Xho1 and BamH1. This produced an EGFP-Jnk1 fusion (SEQ ID NO:44 &45) under the control of a CMV promoter.
- b) The human Jnk1 gene (GenBank Accession number: L26318) was amplified using PCR according to standard protocols with primers Jnk-top (SEQ ID NO:17) and Jnk-bottom/-stop (SEQ ID NO:18). The PCR product was digested with restriction enzymes Xho1 and BamH1, and ligated into pEGFP-N1 (Clontech, Palo Alto; GenBank Accession number U55762) digested with Xho1 and BamH1. This produced a Jnk1-EGFP fusion (SEQ ID NO:62 &63) under the control of a CMV promoter.
- The resulting plasmids are transfected into a suitable cell line, e.g. HEK293, in which the EGFP-Jnk1 probe and/or the Jnk1-EGFP probe should change its cellular distribution from predominantly cytoplasmic to nuclear in response to activation of the signalling pathway with e.g. anisomycin.

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Example 10:

Probes for detection of PKG redistribution.

Useful for monitoring signalling pathways involving changes in cyclic GMP levels, e.g. to identify compounds which modulate the activity of the pathway in living cells.

30 PGK, a cGMP-dependent serine/threonine protein kinase, mediates the guanylyl-cyclase/cGMP signal.

- a) The human PKG gene (GenBank Accession number: Y07512) is amplified using PCR according to standard protocols with primers PKG-top (SEQ ID NO:81) and PKG-bottom/+stop (SEQ ID NO:83). The PCR product is digested with restriction enzymes Xho1 and BamH1, and ligated into pEGFP-C1 (Clontech, Palo Alto; GenBank Accession number U55763) digested with Xho1 and BamH1. This produces an EGFP-PKG fusion (SEQ ID NO:134 &135) under the control of a CMV promoter.
- b) The human PKG gene (GenBank Accession number: Y07512) is amplified using PCR according to standard protocols with primers PKG-top (SEQ ID NO:81) and PKG-bottom/-stop (SEQ ID NO: 82). The PCR product is digested with restriction enzymes Xho1 and BamH1, and ligated into pEGFP-N1 (Clontech, Palo Alto; GenBank Accession number U55762) digested with Xho1 and BamH1. This produces a PKG-EGFP fusion (SEQ ID NO:136 &137) under the control of a CMV promoter.
- The resulting plasmids are transfected into a suitable cell line, e.g. A10, in which the EGFP-PKG probe and/or the PKG-EGFP probe should change its cellular distribution from cyto-plasmic to one associated with cytoskeletal elements within minutes in response to treatment with agents which raise nitric oxide (NO) levels.

Example 11:

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20 Probes for detection of IkappaB kinase redistribution.

Useful for monitoring signalling pathways leading to NFkappaB activation, e.g. to identify compounds which modulate the activity of the pathway in living cells.

IkappaB kinase, a serine/threonine kinase, is a component of a signalling pathway which is activated by a variety of inducers including cytokines, lymphokines, growth factors and stress.

a) The alpha subunit of the human IkappaB kinase gene (GenBank Accession number: AF009225) is amplified using PCR according to standard protocols with primers IKK-top (SEQ ID NO:96) and IKK-bottom/+stop (SEQ ID NO:98). The PCR product is digested with restriction enzymes EcoR1 and Acc65I, and ligated into pEGFP-C1 (Clontech, Palo Alto;

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GenBank Accession number U55763) digested with EcoR1and Acc65I. This produces an EGFP-IkappaB-kinase fusion (SEQ ID NO:120 &121) under the control of a CMV promoter.

b) The alpha subunit of the human IkappaB kinase gene (GenBank Accession number: AF009225) is amplified using PCR according to standard protocols with primers IKK-top (SEQ ID NO:96) and IKK-bottom/-stop (SEQ ID NO:97). The PCR product is digested with restriction enzymes EcoR1 and Acc65I, and ligated into pEGFP-N1 (Clontech, Palo Alto; GenBank Accession number U55762) digested with EcoR1 and Acc65I. This produces an IkappaB-kinase-EGFP fusion (SEQ ID NO:122 &123) under the control of a CMV promoter.

The resulting plasmids are transfected into a suitable cell line, e.g. Jurkat, in which the EGFP-lkappaB-kinase probe and/or the lkappaB-kinase-EGFP probe should achieve a more cytoplasmic distribution within seconds following stimulation with e.g. TNFalpha.

Example 12:

Probes for detection of CDK2 redistribution.

Useful for monitoring signalling pathways of the cell cycle, e.g. to identify compounds which modulate the activity of the pathway in living cells.

CDK2, a cyclin-dependent serine/threonine kinase, is a component of the signalling system which regulates the cell cycle.

- a) The human CDK2 gene (GenBank Accession number: X61622) is amplified using PCR according to standard protocols with primers CDK2-top (SEQ ID NO:102) and CDK2-bottom/+stop (SEQ ID NO: 104). The PCR product is digested with restriction enzymes Xho1 and BamH1, and ligated into pEGFP-C1 (Clontech, Palo Alto; GenBank Accession number U55763) digested with Xho1 and BamH1. This produces an EGFP-CDK2 fusion (SEQ ID NO:114 &115) under the control of a CMV promoter.
 - b) The human CDK2 gene (GenBank Accession number: X61622) is amplified using PCR according to standard protocols with primers CDK2-top (SEQ ID NO:102) and CDK2-bottom/-stop (SEQ ID NO:103). The PCR product is digested with restriction enzymes Xho1 and BamH1, and ligated into pEGFP-N1 (Clontech, Palo Alto; GenBank Accession number U55762) digested with Xho1 and BamH1. This produces a CDK2-EGFP fusion (SEQ ID NO:112 &113) under the control of a CMV promoter.

The resulting plasmids are transfected into a suitable cell line, e.g. HEK293 in which the EGFP-CDK2 probe and/or the CDK2-EGFP probe should change its cellular distribution from cytoplasmic in contact-inhibited cells, to nuclear location in response to activation with a number of growth factors, e.g. IGF.

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Example 13:

Probes for detection of Grk5 redistribution.

Useful for monitoring signalling pathways involving desensitization of G-protein coupled receptors, e.g. to identify compounds which modulate the activity of the pathway in living cells.

Grk5, a G-protein coupled receptor kinase, is a component of signalling pathways involving membrane bound G-protein coupled receptors.

- a) The human Grk5 gene (GenBank Accession number: L15388) is amplified using PCR according to standard protocols with primers Grk5-top (SEQ ID NO:27) and Grk5-bottom/+stop (SEQ ID NO:29). The PCR product is digested with restriction enzymes EcoR1 and BamH1, and ligated into pEGFP-C1 (Clontech, Palo Alto; GenBank Accession number U55763) digested with EcoR1 and BamH1. This produces an EGFP-Grk5 fusion (SEQ ID NO:42 &43) under the control of a CMV promoter.
- b) The human Grk5 gene (GenBank Accession number: L15388) is amplified using PCR according to standard protocols with primers Grk5-top (SEQ ID NO:27) and Grk5-bottom/-stop (SEQ ID NO:28). The PCR product is digested with restriction enzymes EcoR1 and BamH1, and ligated into pEGFP-N1 (Clontech, Palo Alto; GenBank Accession number U55762) digested with EcoR1 and BamH1. This produces a Grk5-EGFP fusion (SEQ ID NO:60 &61) under the control of a CMV promoter.
- The resulting plasmids are transfected into a suitable cell line, e.g. HEK293 expressing a rat dopamine D1A receptor, in which the EGFP-Grk5 probe and/or the Grk5-EGFP probe should change its cellular distribution from predominantly cytoplasmic to peripheral in response to activation of the signalling pathway with e.g. dopamine.

30 Example 14:

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Probes for detection of Zap70 redistribution.

Useful for monitoring signalling pathways involving the T cell receptor, e.g. to identify compounds which modulate the activity of the pathway in living cells.

Zap70, a tyrosine kinase, is a component of a signalling pathway which is active in e.g. T-cell differentiation.

- a) The human Zap70 gene (GenBank Accession number: L05148) is amplified using PCR according to standard protocols with primers Zap70-top (SEQ ID NO:105) and Zap70-bottom/+stop (SEQ ID NO:107). The PCR product is digested with restriction enzymes E-coR1 and BamH1, and ligated into pEGFP-C1 (GenBank Accession number U55763) digested with EcoR1 and BamH1. This produces an EGFP-Zap70 fusion (SEQ ID NO:108 &109) under the control of a CMV promoter.
- b) The human Zap70 gene (GenBank Accession number: L05148) is amplified using PCR according to standard protocols with primers Zap70-top (SEQ ID NO:105) and Zap70-bottom/-stop (SEQ ID NO:106). The PCR product is digested with restriction enzymes E-coR1 and BamH1, and ligated into pEGFP-N1 (Clontech, Palo Alto; GenBank Accession number U55762) digested with EcoR1 and BamH1. This produces a Zap70-EGFP fusion (SEQ ID NO:110 &111) under the control of a CMV promoter.
- The resulting plasmids are transfected into a suitable cell line, e.g. Jurkat, in which the

 EGFP-Zap70 probe and/or the Zap70-EGFP probe should change its cellular distribution
 from cytoplasmic to membrane-associated within seconds in response to activation of the T
 cell receptor signalling pathway with e.g. antibodies to CD3epsilon.

Example 15:

25 Probes for detection of p85 redistribution.

Useful for monitoring signalling pathways involving PI-3 kinase, e.g. to identify compounds which modulate the activity of the pathway in living cells.

p85alpha is the regulatory subunit of Pl3-kinase which is a component of many pathways involving membrane-bound tyrosine kinase receptors and G-protein-coupled receptors.

- a) The human p85alpha gene (GenBank Accession number: M61906) was amplified using PCR according to standard protocols with primers p85-top-C (SEQ ID NO:22) and p85-bottom/+stop (SEQ ID NO:23). The PCR product was digested with restriction enzymes Bgl2 and BamH1, and ligated into pEGFP-C1 (Clontech, Palo Alto; GenBank Accession number U55763) digested with Bgl2 and BamH1. This produced an EGFP-p85alpha fusion (SEQ ID NO:48 &49) under the control of a CMV promoter.
- b) The human p85alpha gene (GenBank Accession number: M61906) was amplified using PCR according to standard protocols with primers p85-top-N (SEQ ID NO:20) and p85-bottom/-stop (SEQ ID NO:21). The PCR product was digested with restriction enzymes E-coR1 and BamH1, and ligated into pEGFP-N1 (Clontech, Palo Alto; GenBank Accession number U55762) digested with EcoR1 and BamH1. This produced a p85alpha-EGFP fusion (SEQ ID NO:66 &67) under the control of a CMV promoter.

The resulting plasmids are transfected into a suitable cell line, e.g. CHO expressing the human insulin receptor, in which the EGFP-p85 probe and/or the p85-EGFP probe may change its cellular distribution from cytoplasmic to membrane-associated within minutes in response to activation of the receptor with insulin.

Example 16:

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Probes for detection of protein-tyrosine phosphatase redistribution.

- Useful for monitoring signalling pathways involving tyrosine kinases, e.g. to identify compounds which modulate the activity of the pathway in living cells.
 - Protein-tyrosine phosphatase1C, a tyrosine-specific phosphatase, is an inhibitory component in signalling pathways involving e.g. some growth factors.
- a) The human protein-tyrosine phosphatase 1C gene (GenBank Accession number: X62055) is amplified using PCR according to standard protocols with primers PTP-top (SEQ ID NO:99) and PTP-bottom/+stop (SEQ ID NO:101). The PCR product is digested with restriction enzymes Xho1 and EcoR1, and ligated into pEGFP-C1 (Clontech, Palo Alto; GenBank Accession number U55763) digested with Xho1 and EcoR1. This produces an EGFP-PTP fusion (SEQ ID NO:116 &117) under the control of a CMV promoter.

WO 98/45704 PCT/DK98/00145

b) The human protein-tyrosine phosphatase 1C gene (GenBank Accession number: X62055) is amplified using PCR according to standard protocols with primers PTP-top (SEQ ID NO:99) and PTP-bottom/-stop (SEQ ID NO:100). The PCR product is digested with restriction enzymes Xho1 and EcoR1, and ligated into pEGFP-N1 (Clontech, Palo Alto; GenBank Accession number U55762) digested with Xho1 and EcoR1. This produces a PTP-EGFP fusion (SEQ ID NO:118 &119) under the control of a CMV promoter.

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The resulting plasmids are transfected into a suitable cell line, e.g. MCF-7 in which the EGFP-PTP probe and/or the PTP-EGFP probe should change its cellular distribution from cytoplasm to the plasma membrane within minutes in response to activation of the growth inhibitory signalling pathway with e.g. somatostatin.

Example 17:

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Probes for detection of Smad4 redistribution.

Useful for monitoring signalling pathways involving most members of the transforming growth factor-beta family, e.g. to identify compounds which modulate the activity of the pathway in living cells.

Smad4, a signal transducer, is a common component of signalling pathways induced by various members of the TGFbeta family of cytokines.

- 20 a) The human Smad4 gene (GenBank Accession number: U44378) was amplified using PCR according to standard protocols with primers Smad4-top and Smad4-bottom/+stop (SEQ ID NO:35). The PCR product was digested with restriction enzymes EcoR1 and BamH1, and ligated into pEGFP-C1 (Clontech, Palo Alto; GenBank Accession number U55763) digested with EcoR1 and BamH1. This produce an EGFP-Smad4 fusion (SEQ ID NO:52 &53) under the control of a CMV promoter.
 - b) The human Smad4 gene (GenBank Accession number: U44378) was amplified using PCR according to standard protocols with primers Smad4-top (SEQ ID NO:33) and Smad4-bottom/-stop (SEQ ID NO:34). The PCR product was digested with restriction enzymes E-coR1 and BamH1, and ligated into pEGFP-N1 (Clontech, Palo Alto; GenBank Accession number U55762) digested with EcoR1 and BamH1. This produced a Smad4-EGFP fusion (SEQ ID NO:76 &77) under the control of a CMV promoter.

The resulting plasmids are transfected into a cell line, e.g. HEK293 in which the EGFP-Smad4 probe and/or the Smad4-EGFP probe should change its cellular distribution within minutes from cytoplasmic to nuclear in response to activation of the signalling pathway with e.g. TGFbeta.

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Example 18:

Probes for detection of Stat5 redistribution.

Useful for monitoring signalling pathways involving the activation of tyrosine kinases of the Jak family, e.g. to identify compounds which modulate the activity of the pathway in living cells.

Stat5, signal transducer and activator of transcription, is a component of signalling pathways which are induced by e.g. many cytokines and growth factors.

- a) The human Stat5 gene (GenBank Accession number: L41142) was amplified using PCR according to standard protocols with primers Stat5-top (SEQ ID NO:30) and Stat5-bottom/+stop (SEQ ID NO:32). The PCR product was digested with restriction enzymes Bgl2 and Acc65I, and ligated into pEGFP-C1 (Clontech; Palo Alto; GenBank Accession number U55763) digested with Bgl2 and Acc65I. This produced an EGFP-Stat5 fusion (SEQ ID NO:54 &55) under the control of a CMV promoter.
- b) The human Stat5 gene (GenBank Accession number: L41142) was amplified using PCR according to standard protocols with primers Stat5-top (SEQ ID NO:30) and Stat5-bottom/stop (SEQ ID NO:331). The PCR product was digested with restriction enzymes Bgl2 and Acc65I, and ligated into pEGFP-N1 (Clontech, Palo Alto; GenBank Accession number U55762) digested with Bgl2 and Acc65I. This produced a Stat5-EGFP fusion (SEQ ID NO:78 &79) under the control of a CMV promoter.

The resulting plasmids are transfected into a suitable cell line, e.g. MIN6 in which the EGFP-Stat5 probe and/or the Stat5-EGFP probe should change its cellular distribution from cyto-plasmic to nuclear within minutes in response to activation signalling pathway with e.g. prolactin.

Example 19:

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Probes for detection of NFAT redistribution.

Useful for monitoring signalling pathways involving activation of NFAT, e.g. to identify compounds which modulate the activity of the pathway in living cells.

- NFAT, an activator of transcription, is a component of signalling pathways which is involved in e.g. immune responses.
 - a) The human NFAT1 gene (GenBank Accession number: U43342) is amplified using PCR according to standard protocols with primers NFAT-top (SEQ ID NO:84) and NFAT-bottom/+stop (SEQ ID NO:86). The PCR product is digested with restriction enzymes Xho1 and EcoR1, and ligated into pEGFP-C1 (Clontech, Palo Alto; GenBank Accession number U55763) digested with Xho1 and EcoR1. This produces an EGFP-NFAT fusion (SEQ ID NO:130 &131) under the control of a CMV promoter.
- b) The human NFAT gene (GenBank Accession number: U43342) is amplified using PCR according to standard protocols with primers NFAT-top (SEQ ID NO:84) and NFAT-bottom/stop (SEQ ID NO:85). The PCR product is digested with restriction enzymes Xho1 and E-coR1, and ligated into pEGFP-N1 (Clontech, Palo Alto; GenBank Accession number U55762) digested with Xho1 and EcoR1. This produces an NFAT-EGFP fusion (SEQ ID NO:132 &133) under the control of a CMV promoter.
- The resulting plasmids are transfected into a suitable cell line, e.g. Jurkat, in which the EGFP-NFAT probe and/or the NFAT-EGFP probe should change its cellular distribution from cytoplasmic to nuclear within minutes in response to activation of the signalling pathway with e.g. antibodies to CD3epsilon.

25 Example 20:

Probes for detection of NFkappaB redistribution.

Useful for monitoring signalling pathways leading to activation of NFkappaB, e.g. to identify compounds which modulate the activity of the pathway in living cells.

NFkappaB, an activator of transcription, is a component of signalling pathways which are responsive to a varity of inducers including cytokines, lymphokines, some immunosuppressive agents.

- a) The human NFkappaB p65 subunit gene (GenBank Accession number: M62399) is amplified using PCR according to standard protocols with primers NFkappaB-top (SEQ ID NO:87) and NFkappaB-bottom/+stop (SEQ ID NO:89). The PCR product is digested with restriction enzymes Xho1 and BamH1, and ligated into pEGFP-C1 (Clontech, Palo Alto; GenBank Accession number U55763) digested with Xho1 and BamH1. This produces an EGFP-NFkappaB fusion (SEQ ID NO:142 & 143) under the control of a CMV promoter.
 - b) The human NFkappaB p65 subunit gene (GenBank Accession number: M62399) is amplified using PCR according to standard protocols with primers NFkappaB-top (SEQ ID NO:87) and NFkappaB-bottom/-stop (SEQ ID NO:88). The PCR product is digested with restriction enzymes Xho1 and BamH1, and ligated into pEGFP-N1 (Clontech, Palo Alto; GenBank Accession number U55762) digested with Xho1 and BamH1. This produces an NFkappaB-EGFP fusion (SEQ ID NO:140 & 141) under the control of a CMV promoter.

The resulting plasmids are transfected into a suitable cell line, e.g. Jurkat, in which the EGFP-NFkappaB probe and/or the NFkappaB-EGFP probe should change its cellular distribution from cytoplasmic to nuclear in response to activation of the signalling pathway with e.g. TNFalpha.

Example 21:

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Probe for detection of RhoA redistribution.

Useful for monitoring signalling pathways involving RhoA, e.g. to identify compounds which modulate the activity of the pathway in living cells.

RhoA, a small GTPase, is a component of many signalling pathways, e.g. LPA induced cytoskeletal rearrangements.

The human RhoA gene (GenBank Accession number: L25080) was amplified using PCR according to standard protocols with primers RhoA-top (SEQ ID NO:92) and RhoA-bottom/+stop (SEQ ID NO:93). The PCR product was digested with restriction enzymes

Hind3 and BamH1, and ligated into pEGFP-C1 (Clontech, Palo Alto; GenBank Accession number U55763) digested with Hind3and BamH1. This produced an EGFP-RhoA fusion (SEQ ID NO:126 &127) under the control of a CMV promoter.

The resulting plasmid is transfected into a suitable cell line, e.g. Swiss3T3, in which the

EGFP-RhoA probe should change its cellular distribution from a reasonably homogenous to
a peripheral distribution within minutes of activation of the signalling pathway with e.g. LPA.

Example 22:

Probes for detection of PKB redistribution.

Useful for monitoring signalling pathways involving PKB e.g. to identify compounds which modulate the activity of the pathway in living cells.

PKB, a serine/threonine kinase, is a component in various signalling pathways, many of which are activated by growth factors.

- a) The human PKB gene (GenBank Accession number: M63167) is amplified using PCR according to standard protocols with primers PKB-top (SEQ ID NO:36) and PKB-bottom/+stop (SEQ ID NO:80). The PCR product is digested with restriction enzymes Xho1 and BamH1, and ligated into pEGFP-C1 (Clontech, Palo Alto; GenBank Accession number U55763) digested with Xho1 and BamH1. This produces an EGFP-PKB fusion (SEQ ID NO:138 & 139) under the control of a CMV promoter.
- b) The human PKB gene (GenBank Accession number: M63167) was amplified using PCR according to standard protocols with primers PKB-top (SEQ ID NO:36) and PKB-bottom/stop (SEQ ID NO:37). The PCR product was digested with restriction enzymes Xho1 and BamH1, and ligated into pEGFP-N1 (Clontech, Palo Alto; GenBank Accession number U55762) digested with Xho1 and BamH1. This produced a PKB-EGFP fusion (SEQ ID NO:70 &71) under the control of a CMV promoter.

The resulting plasmids are transfected into a suitable cell line, e.g. CHO expressing the human insulin receptor, in which the EGFP-PKB probe and/or the PKB-EGFP probe cycles between cytoplasmic and membrane locations during the activation-deactivation process following addition of insulin. The transition should be apparent within minutes.

REFERENCES:

- Adams, S.R., Harootunian, A.T., Buechler, Y.J., Taylor, S.S. & Tsien, R.Y. (1991) Nature 349, 694-697
- Blobe, G.C., Stribling, D.S., Fabbro, D., Stabel, S & Hannun, Y.A. (1996) J. Biol. Chem. 271, 15823-15830
 - Chalfie, M., Tu, Y., Euskirchen, G., Ward, W.W. & Prasher, D.C. (1994) Science **263**, 802-805
 - Cossette, L.J., Hoglinger, O., Mou, L.J. & Shen, S.H. (1997) Exp. Cell Res. 223, 459-466
- DeBernardi, M.A. & Brooker, G. (1996) Proc. Natl. Acad. Sci. USA 93, 4577-4582
 Farese, R.V.. (1992) Biochem. J. 288, 319-323
 - Fulop Jr., T., Leblanc, C., Lacombe, G. & Dupuis, G. (1995) FEBS Lett. 375, 69-74

 Godson, C., Masliah, E., Balboa, M.A., Ellisman, M.H. & Insel, P.A. (1996) Biochem. Biophys. Acta 1313, 63-71
- Khalil, R.A., Lajoie, C., Resnick, M.S. & Morgan, K.G. (1992) American Physiol. Society **c**, 714-719
 - Sano, M., Kohno, M. & Iwanaga, M. (1995) Brain Res. **688**, 213-218

 Bastiaens, P.I.H. & Jovin, T.M. (1996) Proc. Natl. Acad. Sci. USA **93**, 8407-8412

 Schmidt, D.J., Ikebe, M., Kitamura, K., & Fay, F.S. (1997) FASEB J. **11**, 2924 (Abstract)
- Sakai, N., Sasaki, K., Hasegawa, C., Ohkura, M., Suminka, K., Shirai, Y. & Saito, N. (1996) Soc. Neuroscience 22, 69P (Abstract)
 - Sakai, N., Sakai, K. Hasegawa, C., Ohkura, M., Sumioka, ., Shirai, Y., & Naoaki, S. (1997) Japanese Journal of Pharmacology **73**, 69P (Abstract of a meeting held 22-23 March)

SEQUENCE LISTING

5	(1) GENERAL INFORMATION	
	(i) APPLICANT: NovoNordisk, BioImage	
10	(ii) TITLE OF THE INVENTION: A Method of Detecting Cellular Translocation of Biologically Active Polypeptides Using Fluorescense Imaging	
	(iii) NUMBER OF SEQUENCES: 143	
15	(iv) CORRESPONDENCE ADDRESS:(A) ADDRESSEE: NovoNordisk, BioImage(B) STREET: Mørkhøjbygade 28(C) CITY: Søborg	
20	(D) STATE: DK (E) COUNTRY: DENMARK (F) ZIP: 2860	
25	 (v) COMPUTER READABLE FORM: (A) MEDIUM TYPE: Diskette (B) COMPUTER: IBM Compatible (C) OPERATING SYSTEM: DOS (D) SOFTWARE: FastSEQ for Windows Version 2.0 	
	(B) BOTTWARD. TUBEBLY TOT WINDOWS VETSION 200	
30	<pre>(viii) ATTORNEY/AGENT INFORMATION: (A) NAME: , PV&P R (B) REGISTRATION NUMBER:</pre>	
	(C) REFERENCE/DOCKET NUMBER:	
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	GTCTCGAGCC ATCATGAGCA GAAGCAAG	28
35	(2) INFORMATION FOR SEQ ID NO:18:	
	(i) SEQUENCE CHARACTERISTICS:(A) LENGTH: 27 base pairs(B) TYPE: nucleic acid(C) STRANDEDNESS: single	
40	(D) TOPOLOGY: linear	
	(xi) SEQUENCE DESCRIPTION: SEQ ID NO:18:	
45	GTGGATCCCA CTGCTGCACC TGTGCTA	27
	(2) INFORMATION FOR SEQ ID NO:19:	
50	 (i) SEQUENCE CHARACTERISTICS: (A) LENGTH: 28 base pairs (B) TYPE: nucleic acid (C) STRANDEDNESS: single (D) TOPOLOGY: linear 	
55	(with another production and to the to	
	(xi) SEQUENCE DESCRIPTION: SEQ ID NO:19:	

	GTGGATCCTC ACTGCTGCAC CTGTGCTA	•	28
	(2) INFORMATION FOR SEQ ID NO:20:		
5	(i) SEQUENCE CHARACTERISTICS: (A) LENGTH: 40 base pairs		
	(B) TYPE: nucleic acid (C) STRANDEDNESS: single		•
10	(D) TOPOLOGY: linear		•
•			•
	(xi) SEQUENCE DESCRIPTION: SEQ ID NO:20:		
15	CGCGAATTCC GCCACCATGA GTGCTGAGGG GTACCAGTAC		40
	(2) INFORMATION FOR SEQ ID NO:21:		
	(i) SEQUENCE CHARACTERISTICS:		
20	(A) LENGTH: 32 base pairs		
	(B) TYPE: nucleic acid (C) STRANDEDNESS: single		
	(D) TOPOLOGY: linear		
25			
25	(xi) SEQUENCE DESCRIPTION: SEQ ID NO:21:		
	CGCGGATCCT GTCGCCTCTG CTGTGCATAT AC		32
30	(2) INFORMATION FOR SEQ ID NO:22:		
	(i) SEQUENCE CHARACTERISTICS:		
	(A) LENGTH: 30 base pairs(B) TYPE: nucleic acid		
35	(C) STRANDEDNESS: single		
	(D) TOPOLOGY: linear		
	(vi) ORIGINAL SOURCE:		
40	(A) ORGANISM: p85-top-C		
40	(xi) SEQUENCE DESCRIPTION: SEQ ID NO:22:	•	
	GGGAGATCTA TGAGTGCTGA GGGGTACCAG		30
45	(2) INFORMATION FOR SEQ ID NO:23:		
	(i) SEQUENCE CHARACTERISTICS:		
	(A) LENGTH: 34 base pairs		
50	(B) TYPE: nucleic acid(C) STRANDEDNESS: single		
	(D) TOPOLOGY: linear		
	(xi) SEQUENCE DESCRIPTION: SEQ ID NO:23:		
55	GGGCGGATCC TCATCGCCTC TGCTGTGCAT ATAC		34
	Cocooning remembers regressed blue	•	6

	(2) INFORMATION FOR SEQ ID NO:24:		
5	(i) SEQUENCE CHARACTERISTICS:(A) LENGTH: 33 base pairs(B) TYPE: nucleic acid(C) STRANDEDNESS: single(D) TOPOLOGY: linear		
10	(xi) SEQUENCE DESCRIPTION: SEQ ID NO:24:		
	GTGAATTCGA CCATGTCGTC CATCTTGCCA TTC	:	33
15	(2) INFORMATION FOR SEQ ID NO:25:		
20	(i) SEQUENCE CHARACTERISTICS:(A) LENGTH: 31 base pairs(B) TYPE: nucleic acid(C) STRANDEDNESS: single	*	
	(D) TOPOLOGY: linear		
25	(xi) SEQUENCE DESCRIPTION: SEQ ID NO:25:		
20	GTGGTACCCA TGACATGCTT GAGCAACGCA C		31
	(2) INFORMATION FOR SEQ ID NO:26:		
30	(i) SEQUENCE CHARACTERISTICS:(A) LENGTH: 32 base pairs(B) TYPE: nucleic acid(C) STRANDEDNESS: single(D) TOPOLOGY: linear		
35	(b) TOPOLOGI: Tilleat		
	(xi) SEQUENCE DESCRIPTION: SEQ ID NO:26:		
40	GTGGTACCTT ATGACATGCT TGAGCAACGC AC		32
	(2) INFORMATION FOR SEQ ID NO:27:		
45	(i) SEQUENCE CHARACTERISTICS:(A) LENGTH: 31 base pairs(B) TYPE: nucleic acid(C) STRANDEDNESS: single(D) TOPOLOGY: linear		
50 .	(xi) SEQUENCE DESCRIPTION: SEQ ID NO:27:		
	GTGAATTCGT CAATGGAGCT GGAAAACATC G		31
	(2) INFORMATION FOR SEQ ID NO:28:	·	
55	(i) SEQUENCE CHARACTERISTICS:		
			63

	(A) LENGTH: 30 base pairs	
	(B) TYPE: nucleic acid	
	(C) STRANDEDNESS: single	
•	(D) TOPOLOGY: linear	
5	·	
	(xi) SEQUENCE DESCRIPTION: SEQ ID NO:28:	•
	GTGGATCCCT GCTGCTTCCG GTGGAGTTCG	30
10		
•	(2) INFORMATION FOR SEQ ID NO:29:	
	(i) SEQUENCE CHARACTERISTICS:	
	(A) LENGTH: 31 base pairs	
15	(B) TYPE: nucleic acid	
	(C) STRANDEDNESS: single	
	(D) TOPOLOGY: linear	
		•
20	(xi) SEQUENCE DESCRIPTION: SEQ ID NO:29:	
	GTGGATCCCT AGCTGCTTCC GGTGGAGTTC G	31
	(2) INFORMATION FOR SEQ ID NO:30:	•
25		·
	(i) SEQUENCE CHARACTERISTICS:	
	(A) LENGTH: 32 base pairs	
	(B) TYPE: nucleic acid	
	(C) STRANDEDNESS: single	
30	(D) TOPOLOGY: linear	
	(xi) SEQUENCE DESCRIPTION: SEQ ID NO:30:	•
35	GTAGATCTAC CATGGCGGGC TGGATCCAGG CC	32
	(2) INFORMATION FOR SEQ ID NO:31:	
	The state of the same of the s	
	(i) SEQUENCE CHARACTERISTICS:	
40	(A) LENGTH: 31 base pairs	
	(B) TYPE: nucleic acid	
	(C) STRANDEDNESS: single	
	(D) TOPOLOGY: linear	
	(b) lolosoft linear	•
45		•
	(xi) SEQUENCE DESCRIPTION: SEQ ID NO:31:	
	(0-1) ROLLIO	•
	GTGGTACCCA TGAGAGGGAG CCTCTGGCAG A	31
	erotingon tononcodno cererodeno n	31
50	(2) INFORMATION FOR SEQ ID NO:32:	
	(a) intermediation for BEQ 1D NO:32:	
	(i) SEQUENCE CHARACTERISTICS:	
	(A) LENGTH: 31 base pairs	
	(B) TYPE: nucleic acid	
55	(C) STRANDEDNESS: single	
	(D) TOPOLOGY: linear	
	(b) totohoot. Tilledi	

	(xi) SEQUENCE DESCRIPTION: SEQ ID NO:32:	
5	GTGGTACCTC ATGAGAGGGA GCCTCTGGCA G	31
	(2) INFORMATION FOR SEQ ID NO:33:	
10	(i) SEQUENCE CHARACTERISTICS:(A) LENGTH: 33 base pairs(B) TYPE: nucleic acid(C) STRANDEDNESS: single(D) TOPOLOGY: linear	
15	(xi) SEQUENCE DESCRIPTION: SEQ ID NO:33:	
	GTGAATTCAA CCATGGACAA TATGTCTATT ACG	33
20	(2) INFORMATION FOR SEQ ID NO:34:	
25	 (i) SEQUENCE CHARACTERISTICS: (A) LENGTH: 31 base pairs (B) TYPE: nucleic acid (C) STRANDEDNESS: single (D) TOPOLOGY: linear 	
30	(xi) SEQUENCE DESCRIPTION: SEQ ID NO:34: GTGGATCCCA GTCTAAAGGT TGTGGGTCTG C	31
	(2) INFORMATION FOR SEQ ID NO:35:	
35	 (i) SEQUENCE CHARACTERISTICS: (A) LENGTH: 32 base pairs (B) TYPE: nucleic acid (C) STRANDEDNESS: single (D) TOPOLOGY: linear 	
40		
	(xi) SEQUENCE DESCRIPTION: SEQ ID NO:35: GTGGATCCTC AGTCTAAAGG TTGTGGGTCT GC	32
45	(2) INFORMATION FOR SEQ ID NO:36:	
50	(i) SEQUENCE CHARACTERISTICS:(A) LENGTH: 27 base pairs(B) TYPE: nucleic acid	
	(C) STRANDEDNESS: single (D) TOPOLOGY: linear	
55	(xi) SEQUENCE DESCRIPTION: SEQ ID NO:36:	

WO 98/45704 PCT/DK98/00145

	GTCTCGAGGC ACCATGAGCG ACGTGGC	27												
	(2) INFORMATION FOR SEQ ID NO:37:													
5	 (i) SEQUENCE CHARACTERISTICS: (A) LENGTH: 27 base pairs (B) TYPE: nucleic acid (C) STRANDEDNESS: single (D) TOPOLOGY: linear 													
10	(b) Torobodi. Timeat													
	(xi) SEQUENCE DESCRIPTION: SEQ ID NO:37:													
	TGGGATCCGA GGCCGTGCTG CTGGCCG	27												
15	(2) INFORMATION FOR SEQ ID NO:38:													
20	 (i) SEQUENCE CHARACTERISTICS: (A) LENGTH: 1896 base pairs (B) TYPE: nucleic acid (C) STRANDEDNESS: single (D) TOPOLOGY: linear 													
25	(ii) MOLECULE TYPE: cDNA (ix) FEATURE:													
30	(A) NAME/KEY: Coding Sequence(B) LOCATION: 11891(D) OTHER INFORMATION:(xi) SEQUENCE DESCRIPTION: SEQ ID NO:38:													
35	ATG GTG AGC AAG GGC GAG GAG CTG TTC ACC GGG GTG GTG CCC ATC CTG Met Val Ser Lys Gly Glu Glu Leu Phe Thr Gly Val Val Pro Ile Leu 1 5 10 15	48												
	GTC GAG CTG GAC GGC GAC GTA AAC GGC CAC AAG TTC AGC GTG TCC GGC Val Glu Leu Asp Gly Asp Val Asn Gly His Lys Phe Ser Val Ser Gly 20 25 30	96												
40	GAG GGC GAG GGC GAT GCC ACC TAC GGC AAG CTG ACC CTG AAG TTC ATC Glu Gly Glu Gly Asp Ala Thr Tyr Gly Lys Leu Thr Leu Lys Phe Ile 35 40 45	144												
45	TGC ACC ACC GGC AAG CTG CCC GTG CCC TGG CCC ACC CTC GTG ACC ACC Cys Thr Thr Gly Lys Leu Pro Val Pro Trp Pro Thr Leu Val Thr Thr 50 55 60	192												
50	CTG ACC TAC GGC GTG CAG TGC TTC AGC CGC TAC CCC GAC CAC ATG AAG Leu Thr Tyr Gly Val Gln Cys Phe Ser Arg Tyr Pro Asp His Met Lys 65 70 75 80	240												
55	CAG CAC GAC TTC TTC AAG TCC GCC ATG CCC GAA GGC TAC GTC CAG GAG Gln His Asp Phe Phe Lys Ser Ala Met Pro Glu Gly Tyr Val Gln Glu 85 90 95	288												

									GCC Ala		336
5									AAG Lys		384
10	 								GAG Glu	•	432
15									AAG Lys		480
									GGC Gly 175		528
20									GAC Asp		576
25									GCC Ala		624
30									GAG Glu		672
35									AAG Lys		720
40			Ala			Ser			GCG Ala 255		768
40									GGG Gly		816
45					Glu				CCG Pro		864
50								Gly		GCG Ala	912
55	Gly			Ala			Arg			GTG Val 320	960

										00							
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.			u AL	34	0	e GII	1 116	s re	u Lei 345	u Arg	g Ph	e Ar	g His	350	ı Ası)	r GTC n Val	1056
10		. 01	35	5	g Ası	ò IIE	: Lev	360	g Ala	a Sei	Thi	r Lei	1 Glu 365	ı Ala	Met	G AGA C Arg	1104
15	,,,,,	37	0	r 11.	e vaj	GIN	375	Lev	ı Met	Glu	Thr	380	Leu)	Туг	Lys	TTG Leu	1152
20	385		a se.	C GII	. GII	з <u>ье</u> и 390	ser	Asn	Asp	His	395	: Cys	Tyr	Phe	Leu	TAC Tyr 400	1200
	011		e net	ALC	405		гуѕ	Tyr	Ile	His 410	Ser	Ala	Asn	Val	Leu 415	His	1248
25	Arg	Lan	, ner	420	Pro	TCC	Asn	Leu	Leu 425	Ser	Asn	Thr	Thr	Cys 430	Asp	Leu	1296
30		110	435	Asp	Pne	GGC Gly	Leu	A1a 440	Arg	Ile	Ala	Asp	Pro 445	Glu	His	Asp	1344
35	*****	450	Gly	PHE	nea	ACG Thr	455	Tyr	Val	Ala	Thr	Arg 460	Trp	Tyr	Arg	Ala	1392
40	465	Olu	116	Met	Leu	AAC Asn 470	ser	гуѕ	Gly	Tyr	Thr 475	Lys	Ser	Ile	Asp	Ile 480	1440
		DCI	val	GIY	485	ATT Ile	ьеп	Ala	Glu	Met 490	Leu	Ser	Asn	Arg _.	Pro 495	Ile	1488
45	TTC Phe	CCT Pro	GGC Gly	AAG Lys 500	CAC His	TAC Tyr	CTG Leu	GAT Asp	CAG Gln 505	CTC Leu	AAC Asn	CAC His	Ile	CTG Leu 510	GGC Gly	ATC Ile	1536
50	CTG Leu	GGC Gly	TCC Ser 515	CCA Pro	TCC Ser	CAG (Gln (31u A	GAC Asp 520	CTG .	AAT Asn	TGT Cys	Ile	ATC Ile 525	AAC Asn	ATG . Met	AAG Lys	1584
55	,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,,	CGA Arg 530	AAC Asn	TAC Tyr	CTA Leu	CAG :	CT (Ser 1	CTG (Leu :	CCC '	TCC :	Lys	ACC Thr 540	AAG (Lys	GTG (Val)	GCT Ala	TGG Trp	1632

WO 98/45704 PCT/DK98/00145

										69		•					
														CTG Leu			1680
5														GAG Glu			1728
10														GAT Asp 590			1776
15												Leu		GAC Asp			1824
20														CGC Arg			1872
		GGA Gly				_		CTAG									1896
25	5 (2) INFORMATION FOR SEQ ID NO:39:																
30	(i) SEQUENCE CHARACTERISTICS:(A) LENGTH: 631 amino acids(B) TYPE: amino acid(C) STRANDEDNESS: single(D) TOPOLOGY: linear														•		
35		7)	7) FI	RAGMI	ENT :	TYPE:	int	rote: terna	al		V O. 1						
		()	(T) s	PEQUI	ENCE	DESC	JRIP.	rion	: SE	עד נ	NO:	39:					
40	Met 1	Val	Ser	Lys	Gly 5	Glu	Glu	Leu	Phe	Thr 10	Gly	Val	Val	Pro	Ile 15	Leu	
	Val	Glu	Leu	Asp 20	Gly	Asp	Val	Asn	Gly 25	His	Lys	Phe	Ser	Val 30	Ser	Gly	
	Glu	Gly	Glu 35		Asp	Ala	Thr	Tyr 40		Lys	Leu	Thr	Leu 45	Lys	Phe	Ile	
45	Сув	Thr 50		Gly	Lys	Leu	Pro		Pro	Trp	Pro	Thr		Val	Thr	Thr	
	Leu 65	-	Tyr	Gly	Val	Gln 70		Phe	Ser	Arg	Tyr 75		Asp	His	Met	Lys 80	
50		His	Asp	Phe	Phe 85	-	Ser	Ala	Met	Pro		Gly	Tyr	Val	Gln 95	Glu	
	Arg	Thr	Ile	Phe		Lys	Asp	Asp	Gly 105	-	Tyr	Lys	Thr	Arg	-	Glu	
	Val	Lys	Phe		Gly	Asp	Thr	Leu 120		Asn	Arg	Ile	Glu 125		Lys	Gly	
55	Ile	Asp 130		Lys	Glu	Asp	Gly 135		Ile	Leu	Gly	His 140		Leu	Glu	Tyr	
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WO 98/45704 PCT/DK98/00145

	Asn 145	Tyr	Asn	Ser	His	Asn 150	Val	Tyr	Ile	Met	Ala 155	Asp	Lys	Gln	ГÀВ	Asn 160
	Gly	Ile	Lys	Val	Asn 165	Phe	Lys	Ile	Arg	His 170	Asn	Ile	Glu	Asp	Gly 175	Ser
5	Val	Gln	Leu	Ala 180	Asp	His	Tyr	Gln	Gln 185	Asn	Thr	Pro	Ile	Gly 190	Asp	Gly
	Pro	Val	Leu 195	Leu	Pro	Asp	Asn	His 200	Tyr	Leu	Ser	Thr	Gln 205	Ser	Ala	Leu
10	Ser	Lys 210	Asp	Pro	Asn	Glu	Lys 215	Arg	Asp	His	Met	Val 220	Leu	Leu	Glu	Phe
	Val 225	Thr	Ala	Ala	Gly	Ile 230	Thr	Leu	Gly	Met	Asp 235	Glu	Leu	Tyr	Lys	Ser 240
	Gly	Leu	Arg	Ser	Arg 245	Ala	Gln	Ala	Ser	Asn 250	Ser	Thr	Met	Ala	Ala 255	Ala
15	Ala	Ala	Gln	Gly 260	Gly	Gly	Gly	Gly	Glu 265	Pro	Arg	Arg	Thr	Glu 270	Gly	Val
			275					280				_	285	Gln		
20	Asp		Gly	Pro	Arg	Tyr	Thr 295	Gln	Leu	Gln	Tyr	Ile 300	Gly	Glu	Gly	Ala
	305	_				310		_			315		_	Thr	_	320
					325		•			330				Cys	335	•
25				340					345			•		Glu 350		
		_	.355	_				360					365	Ala		•
30	-	370					375					380		Tyr		
	385					390			_		395		_	Phe		400
					405			_		410				Val	415	
35		_		420					425					Cys 430		
			435					440					445			
40		450					455	_				460	_	Tyr		
	465					470					475			Ile -		4.80
					485					490				Arg	495	
45				500					505					Leu 510		
			515					520			_		525	Asn		
50		530					535				_	540		Val		
	545	_				550				-	555			Leu		560
					565				_	570				Glu	575	
55	Leu	Ala	nis	Pro	ıyr	Leu	GIU	GIN	Tyr	туг	Asp	Pro	Thr	Asp	GIU	PTC

	Val	Ala	Glu 595	Glu	Pro	Phe	Thr	Phe 600	Ala	Met	Glu		Asp 605	Asp	Leu	Pro	
	Lys	Glu		Leu	Lys	Glu	Leu		Phe	Gln	Glu			Arg	Phe	Gln	
_	5	610	17- 1	T 011	a1	77.	615					620					
5	Pro 625	Gly	vaı	ьeп	GIU	630	Pro										
			(5)									-					
			(2)	INF	ORMA	TION	FOR	SEÇ	D	NO : 4	0:						
10		(i		QUEN												•	
				LENG				_	irs								
•				STRA					:								
15			(D)	TOPO	LOGY	7: li	near	•									
15		(i	.i) M	OLEC	ULE	TYPE	: cI	ANO			ţ	,					
		(i	.x) F	EATU	JRE:												
			(A)	NAM	iE/KE	EY: C	odir	ıg Se	quen	ce							
20				LOC													
			(D)	OTH	ier i	INFOR	(MAT.)	ON:									
		(>	ci) S	EQUE	ENCE	DESC	RIPT	: NOI	SEC) ID	NO:4	0:					
25	ATG	GTG	AGC	AAG	GGC	GAG	GAG	CTG	TTC	ACC	GGG	GTG	GTG	CCC	ATC	CTG	48
		Val	Ser	Lys		Glu	Glu	Leu	Phe		Gly	Val	Val	Pro		Leu	
	1				5					10					15		
		GAG															96
30	Val	Glu	Leu	Asp 20	Gly	Asp	Val	Asn	Gly 25	His	Lys	Phe	Ser	Val	Ser	Gly	
	•																
		GGC Gly															144
35	Giu	Gry	35	GIY	Asp	AIG	1111	40	GIA	цув	Dea	1111	45	LJ 5	1 110		
	maa.	ACC	אככ	ccc	א א כר	OTC	ccc	CTC	ccc	TCC	ccc	אַמַּמ	CTC	GTG	ACC	ACC	192
		Thr															174
40	_	50					55					60					
40	CTG	ACC	TAC	GGC	GTG	CAG	TGC	TTC	AGC	CGC	TAC	CCC	GAC	CAC	ATG	AAG	240
	Leu	Thr				Gln					Tyr					Lys	
	65					70					.75					80	
45		CAC															288
	Gln	His	Asp	Phe	Phe 85	Lys	Ser	Ala	Met	Pro 90	Glu	Gly	Tyr	Val	Gln 95	Glu	
					0.5					90					,,		
50		ACC															336
50	Arg	Thr	тте	100	PHE	пур	изр	нар	105	ASI	īŸĽ	пλя	THE	110	wra		
			m=-	~ ~ ~	ac-	03.0	200	om-	a=-		~~~	N mc	<i>~</i> ~	ama	7 7 C	000	
		AAG Lys															384
55	. ===	4 -	115		•	•		120			J		125		-	-	

	GAC Asp 130										432
5	TAC Tyr			Val							480
10	ATC Ile										528
15	CAG Gln										576
20	GTG Val										624
	 AAA Lys 210										672
25	ACC Thr										720
30	CTC Leu								_		768
35	ATG Met										816
40	TCG Ser				Tyr						864
40	AAT Asn 290										912
45	CAC His										960
50	CGC Arg									Arg	1008
55	CCA Pro					Val			Asp		1056

																	•
	ATG	GAG	ACA	GAT	CTT	TAC	AAG	CTC	TTG	AAG	ACA	CAG	CAC	CTC	AGC	AAT	1104
														Leu			
		-	355	•		•	•	360	•	•			365				
5	GAT	CAT	ATC	TGC	TAT	TTT	CTT	TAT	CAG	ATC	CTG	AGA	GGA	TTA	AAG	TAT	1152
_														Leu			
	p	370		-,-	-7-		375	-1-				380	1		-,-	-1-	
, ,		3,0					3.3										
	מדמ	СЪТ	TCA	GCT	Тαα	GTT	CTG	CAC	CGT	GAC	СТС	AAG	ССТ	TCC	AAC	CTC	1200
10														Ser			
	385	****	001	1114		390			••••	110p	395	2,5			11011	400	
	505																
	CTG	CTG	AAC	ACC	ACT	TGT	GAT	CTC	AAG	ATC	TGT	GAC	TTT	GGC	CTT	GCC	1248
														Gly			
15	200				405	-1-	<u>F</u>		-1-	410	-7			1	415		
10																	
	ССТ	GTT	GCA	GAT	CCA	GAC	CAT	GAT	CAT	ACA	GGG	TTC	TTG	ACA	GAG	TAT	1296
														Thr			
	AL 9	var	mu	420		тър	1110	p	425					430	<u> </u>	-1-	
20				120					123					130			
20	GTA	GCC	ACG	ССТ	TGG	тас	ΣGΣ	GCT	CCA	AAD	ΔΤΤ	ΔTG	ጥጥር፤	AAT	TCC	DAG	1344
														Asn			
	VUI	niu	435	••••	P	-1-	•••	440		014		1100	445				•
			173					110					11.0				
25	GGT	тат	ACC	DAG	TCC	АТТ	GAT	ATT	TGG	тст	GTG	GGC	TGC	ATC	CTG	GCA	1392
																Ala.	
		450		-,-			455		F			460	-1-				
				•													
	GAG	ATG	CTA	TCC	AAC	AGG	CCT	ATC	TTC	CCA	GGA	AAG	CAT	TAC	CTT	GAC	1440
30		_												Tyr			
	465					470					475					480	
	CAG	CTG	TAA	CAC	ATC	CTG	GGT	TTA	CTT	GGA	TCT	CCA	TCA	CAG	GAA	GAT	1488
	Gln	Leu	Asn	His	Ile	Leu	Gly	Ile	Leu	Gly	Ser	Pro	Ser	Gln	Glu	Asp	
35					485		-			490					495		
	CTG	TAA	TGT	ATA	ATA	AAT	TTA	AAA	GCT	AGA	AAC	TAT	TTG	CTT	TCT	CTC	1536
	Leu	Asn	Сув	Ile	Ile	Asn	Leu	Lys	Ala	Arg	Asn	Tyr	Leu	Leu	Ser	Leu	
			-	500				_	505	_		-		510			
40																	
	CCG	CAC	AAA	AAT	AAG	GTG	CCG	TGG	AAC	AGG	TTG	TTC	CCA	AAC	GCT	GAC	1584
	Pro	His	Lys	Asn	Lys	Val	Pro	Trp	Asn	Arq	Leu	Phe	Pro	Asn	Ala	Asp	
			515		-			520	,	_			525			_	
													•				
45	TCC	AAA	GCT	CTG	GAT	TTA	CTG	GAT	AAA	ATG	TTG	ACA	TTT	AAC	CCT	CAC	1632
	Ser	Lys	Ala	Leu	Asp	Leu	Leu	Asp	Lys	Met	Leu	Thr	Phe	Asn	Pro	His	
		530			_		535	_	-			540					
	AAG	AGG	TTA	GAA	GTT	GAA	CAG	GCT	CTG	GCC	CAC	CCG	TAC	CTG	GAG	CAG	1680
50	Lys	Arg	Ile	Glu	Val	Glu	Gln	Ala	Leu	Ala	His	Pro	Tyr	Leu	Glu	Gln	
	545					550					555		-			560	
	TAT	TAT	GAC	CCA	AGT	GAT	GAG	CCC	ATT	GCT	GAA	GCA	CCA	TTC	AAG	TTT	1728
	Tyr	Tyr	Asp	Pro	Ser	Asp	Glu	Pro	Ile	Ala	Glu	Ala	Pro	Phe	Lys	Phe	
55	-	=			565					570					575		

										14							
		ATG Met															1776
5		GAA Glu												TAA			1818
0	•		(2)	INF	ORMA	MOITA	I FOR	SEÇ	Q ID	NO:4	1:						
		(i	(A) (B)	EQUEN LENG TYPE	TĤ: : an	605 nino	amir acio	no ao 1	cids								
15				STRA				_	9								
				OLEC			_										
20		·	•	EQUE						מו כ	NO:4	11:					
	Met 1	Val	Ser	Lys	Gly 5	Glu	Glu	Leu	Phe	Thr 10	Gly	Val	Val	Pro	Ile 15	Leu	
25	Val	Glu	Leu	Asp 20	Gly	Asp	Val	Asn	Gly 25	His	Lys	Phe	Ser	Val 30	Ser	Gly	
	Glu	Gly	Glu 35	Gly	Авр	Ala	Thr	Tyr 40	Gly	Lys	Leu	Thr	Leu 45	Lys	Phe	Ile	
30	-	Thr 50					55					60					
	65	Thr	_	_		70	-				75					80	
		His	_		85	_				90					95		
35	_	Thr		100					105					110			
		Lys	115		_		. ,	120			, -		125				
40		Asp 130					135					140					
	Asn 145	Tyr	Asn	Ser	His	Asn 150	Val	Tyr	Ile	Met	Ala 155	Asp	Lys	Gln	Lys	Asn 160	
		Ile	Lys	Val	Asn 165		Lys	Ile	Arg	His 170	Asn	Ile	Glu	Asp	Gly 175		
45	Val	Gln	Leu	Ala 180	Asp	His	Tyr	Gln	Gln 185	Asn	Thr	Pro	Ile	Gly 190		Gly .	
	Pro	Val	Leu 195	Leu	Pro	Asp	Asn	His 200		Leu	Ser	Thr	Gln 205		Ala	Leu	
50	Ser	Lys 210	-	Pro	Asn	Glu	Lys 215	Arg	Asp	His	Met	Val 220		Leu	Glu	Phe	
			Ala	Ala	Gly		Thr	Leu	Gly	Met			Leu	Tyr	Lys	Ser	
	225 Gly		Arg	Ser		230 Val	Thr	Met	Ala		235 Ala		Ala	Ala		240 Pro	
55	Glu	Met	Val	_	245 Gly	Gln	Val	Phe	_		Gly	Pro	Arg			Asn	
				260					265					270			

```
Leu Ser Tyr Ile Gly Glu Gly Ala Tyr Gly Met Val Cys Ser Ala Tyr
                                  280
     Asp Asn Leu Asn Lys Val Arg Val Ala Ile Lys Lys Ile Ser Pro Phe
                              295
                                                  300
5
     Glu His Gln Thr Tyr Cys Gln Arg Thr Leu Arg Glu Ile Lys Ile Leu
                         310
                                              315
     Leu Arg Phe Arg His Glu Asn Ile Ile Gly Ile Asn Asp Ile Ile Arg
                      325
                                          330
     Ala Pro Thr Ile Glu Gln Met Lys Asp Val Tyr Ile Val Gln Asp Leu
10
                                      345
     Met Glu Thr Asp Leu Tyr Lys Leu Leu Lys Thr Gln His Leu Ser Asn
     Asp His Ile Cys Tyr Phe Leu Tyr Gln Ile Leu Arg Gly Leu Lys Tyr
                              375
15
     Ile His Ser Ala Asn Val Leu His Arg Asp Leu Lys Pro Ser Asn Leu
                          390
                                              395
     Leu Leu Asn Thr Thr Cys Asp Leu Lys Ile Cys Asp Phe Gly Leu Ala
                      405
                                          410
     Arg Val Ala Asp Pro Asp His Asp His Thr Gly Phe Leu Thr Glu Tyr
20
                  420
                                      425
     Val Ala Thr Arg Trp Tyr Arg Ala Pro Glu Ile Met Leu Asn Ser Lys
                                  440
     Gly Tyr Thr Lys Ser Ile Asp Ile Trp Ser Val Gly Cys Ile Leu Ala
                              455
                                                  460
25
     Glu Met Leu Ser Asn Arg Pro Ile Phe Pro Gly Lys His Tyr Leu Asp
                          470
                                              475
      Gln Leu Asn His Ile Leu Gly Ile Leu Gly Ser Pro Ser Gln Glu Asp
                      485
                                          490
      Leu Asn Cys Ile Ile Asn Leu Lys Ala Arg Asn Tyr Leu Leu Ser Leu
30
                  500
                                      505
      Pro His Lys Asn Lys Val Pro Trp Asn Arg Leu Phe Pro Asn Ala Asp
                                  520
      Ser Lys Ala Leu Asp Leu Leu Asp Lys Met Leu Thr Phe Asn Pro His
                              535
                                                  540
35
      Lys Arg Ile Glu Val Glu Gln Ala Leu Ala His Pro Tyr Leu Glu Gln
                          550
                                              555
      Tyr Tyr Asp Pro Ser Asp Glu Pro Ile Ala Glu Ala Pro Phe Lys Phe
                      565
                                          570
      Asp Met Glu Leu Asp Asp Leu Pro Lys Glu Lys Leu Lys Glu Leu Ile
40
                                      585
      Phe Glu Glu Thr Ala Arg Phe Gln Pro Gly Tyr Arg Ser
                                  600
```

(2) INFORMATION FOR SEQ ID NO:42:

45

- (i) SEQUENCE CHARACTERISTICS:
 - (A) LENGTH: 2529 base pairs
 - (B) TYPE: nucleic acid
 - (C) STRANDEDNESS: single
 - (D) TOPOLOGY: linear
- (ii) MOLECULE TYPE: cDNA
- (ix) FEATURE:
- 55 (A) NAME/KEY: Coding Sequence
 - (B) LOCATION: 1...2526

(D) OTHER INFORMATION:

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:42:

5	GTG Val								CTG Leu	48
10	GAG Glu									96
15	GGC Gly									144
	 ACC Thr 50									192
20	ACC Thr									240
25	 CAC His									288
30	ACC Thr									336
35	AAG Lys								_	384
40	GAC Asp 130									432
	TAC Tyr									480
45	ATC Ile									528
50	CAG Gln									_. 576
55	GTG Val				Tyr			Ser		624

						• •					•
		CCC Pro									672
5		GCC Ala									720
10		TCT Ser								•	768
15		GCC Ala 260								GGA Gly	816
20		AAA Lys									864
20		AGC Ser						•			912
25		TTA Leu		Lys							960
30		GAA Glu									1008
35		GCA Ala 340									1056
40		GAA Glu									1104
		CAA Gln									1152
45		AAG Lys									1200
50		TAC Tyr									1248
55		GAC Asp 420									1296

		Thr				TAT Tyr				_		1344
5						GTT Val						1392
10	GCC Ala 465					AGG Arg						1440
15						ATC Ile						1488
20						TAC Tyr 505						1536
						GGT Gly						1584
25						GAG Glu						1632
30						GAC Asp						1680
35						ATC Ile						1728
40						GCT Ala 585						1776
											GTC Val	1824
45									Trp		GGC Gly	1872
50		Leu			Ile			Pro			CGT Arg 640	1920
55							Arg				ACG Thr	1968

										ATC Ile	2016
5										CAG Gln	2064
10										ATG Met	2112
15	Lys									CCA Pro	2160
20										TTC Phe 735	.2208
20	-									TAC Tyr	2256
25										ATG Met	2304
30										GGT Gly	2352
35						•				AAG Lys	2400
10										TCC Ser 815	2448
40										TCA Ser	2496
45	GTC Val				 			TAG			2529
50		(2)	· INI	ATIO		Q ID	NO:	13:			•

- (i) SEQUENCE CHARACTERISTICS:
 - (A) LENGTH: 842 amino acids
 - (B) TYPE: amino acid
 - (C) STRANDEDNESS: single
 - (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein (v) FRAGMENT TYPE: internal

5 (xi) SEQUENCE DESCRIPTION: SEQ ID NO:43:

•	Met 1	Val	Ser	Lys	Gly 5	Glu	Glu	Leu	Phe	Thr 10	Gly	Val	Val	Pro	Ile 15	Leu
10	Val	Glu	Leu	Asp 20	Gly	Asp	Val	Asn	Gly 25	His	Lys	Phe	Ser	Val 30	Ser	Gly
	Glu	Gly	Glu 35	Gly	Asp	Ala	Thr	Tyr 40	Gly	Lys	Leu	Thr	Leu 45	Lys	Phe	Ile
	Cys	Thr 50	Thr	Gly	Lys	Leu	Pro 55	Val	Pro	Trp	Pro	Thr 60	Leu	Val	Thr	Thr
15	Leu 65	Thr	Tyr	Gly	Val.	Gln 70	Cys	Phe	Ser	Arg	Tyr 75	Pro	Asp	His	Met	Lys 80
	Gln	His	Asp	Phe	Phe 85	rys	Ser	Ala	Met	Pro 90	Glu	Gly	Tyr	Val	Gln 95	Glu
20	Arg	Thr	Ile	Phe 100		Lys	Asp	Asp	Gly 105	Asn	Tyr	Lys	Thr	Arg 110	Ala	Glu
		-	115			_		120	•		_		125		Lys	
		130					135					140			Glu	
25	145					150		_			155				Ĺys	160
	-		_		165		_			170					Gly 175	
30				180					185					190	Asp	
			195					200					205.		Ala	
		210	-				215		_			220			Glu	
35	225					230			_		235				Lys	240
	_				245					250					Leu 255	
40				260					265					270	Gly	
	_		275					280					285		Lys	
		290					295					300			Arg	
45	305					310					315				Phe	320
					325					330					Phe 335	
50 .	_			340					345					350		
	_	_	355					360	-				365		Pro	
		370					375	_				380			Glu	
55	Leu 385		Gln	Lys	Pro	Cys 390		Glu	Leu	Phe	Ser 395		Cys	Ala	Gln	Ser 400

	Val	His	Glu	Tyr	Leu 405	Arg	Gly	Glu	Pro	Phe	His	Glu	Tyr	Leu	Asp 415	Ser
	Met	Phe	Phe	Asp 420	Arg	Phe	Leu	Gln	Trp 425		Trp	Leu	Glu	Arg 430		Pro
5			435		Thr			440					445			_
		450			Cys		455					460	_			-
10	465				Leu	470					475				_	480
					Asn. 485					490					495	
4.5				500	Leu				505					510		
15			515		Ile			520					525			=
		530			Pro Cys		535					540				
20	545				Lys	550					555					560
		•			565 Asp			•		570			_	-	575	
25				580	Arg				585		_			590	_	_
			595		Arg			600					605			
		610			Glu		615				_	620	_	_		
30	625				Lys	630					635			_	_	640
					645 Ser					650					655	
35	Lys	Met	Leu	660 Leu	Thr	Lys	Asp	Ala	665 Lys	Gln	Arg	Leu	Gly	670 Cys	Gln	Glu
	Glu	Gly	675 Ala	Ala	Glu	Val	Lys	680 Arg	His	Pro	Phe	Phe	685 Arg	Asn	Met	Asn
0.2		690 Lys	Arg	Leu	Glu	Ala	695 Gly	Met	Leu	Asp	Pro	700 Pro	Phe	Val	Pro	qaA
40	705 Pro	Arg	Ala	Val	Tyr	710 Cys		Asp	Val	Leu	715 Asp	Ile	Glu	Gln		720 Ser
	Thr	Val	Lys		725 Val	Asn	Leu	Asp		730 Thr	Asp	Asp	Asp		735 Tyr	Ser
45	Lys	Phe	Ser 755	740 Thr	Gly	Ser	Val		745 Ile	Pro	Trp	Gln		750 Glu	Met	Ile
	Glu	Thr 770		Cys	Phe	Lys	Glu 775	760 Leu	Asn	Val	Phe		765 Pro	Asn	Gly	Thr
50	Leu 785		Pro	Asp	Leu	Asn 790		Asn	His	Pro	Pro 795	780 Glu	Pro	Pro	Lys	Lys 800
		Leu	Leu	Gln	Arg 805		Phe	Lys	Arg	Gln 810		Gln	Asn	Asn	Ser 815	
	Ser	Ser	Pro	Ser 820	Ser	Lys	Thr	Ser	Phe 825		His	His	Ile	Asn 830		Asn
55	His		Ser 835	Ser	Asn	Ser	Thr	Gly 840		Ser						

(2) INFORMATION FOR SEQ ID NO:44:

10		Ė)	(A) (B) (C) (D) (ii) N (x) H	LENC TYPE STRA TOPO MOLEC FEATU	ETH: NUDEL OLOGY CULE JRE:	CHARA 1902 1Clei DNESS 7: li TYPE EY: C	2 bas c ac c si inear E: cI	se pa cid ingle C DNA	airs	ice							
15						INFOR											
		()	d) s	SEOU	MCE	DESC	ים ד סי	רד האז	: SEC	מד נ	NO · 4	14.	•				
		()	(1)	JEQUI	SINCE	טננט	-KIF	LION	. 564	עב ג	NO. 5						
20									TTC Phe								48
20	1	Val	261	nys	,G1 y	Giu	GIU	пец	PILE	10	Gry	vai	vai	PIO	15	пец	
	CTC.	CAC	CTC	CAC	ccc	CNC	CTD	7 7 C	GGC	CZC	. 3. 3. 67	TO TO	אממ	CTC	TOO	ccc	96
									Gly								96
25				20	_	_			25		-			30			
	GAG	GGC	GAG	GGC	GAT	GCC	ACC	TAC	GGC	AAG	CTG	ACC	CTG	AAG	TTC	ATC	144
									Gly								
30			35				•	40					45				
30	TGC	ACC	ACC	GGC	AAG	CTG	CCC	GTG	CCC	TGG	ccc	ACC	CTC	GTG	ACC	ACC	192
	Cys		Thr	Gly	Lys	Leu		Val	Pro	Trp	Pro		Leu	Val	Thr	Thr	
		50					55					60					
35									AGC								240
	Leu 65	Thr	Tyr	Gly	Val	Gln 70	Cys	Phe	Ser	Arg	Tyr 75	Pro	Asp	His	Met	Lys 80	
	65										/5					80	
40									ATG								288
40	GIn	His	Asp	Pne	Pne 85	гÀв	ser	Ala	Met	Pro 90	GIu	GIA	ıyr	vaı	95	GIU	
					•												
									GGC Gly								336
45	Arg	. 1111	116	100	FILE	Був	veħ	veb	105	ASII	LYL	Буб	1111	110	ALG	Olu	
			mma			a. a		c==					~~~	oma		999	204
									GTG Val							Gly	384
		-1-	115		1	L		120			5		125				
50	N.T.C	ana	mma	220	an a	an a	000	220	» m.c	ama	222	an a	220	ama	CAC	TT A CT	430
									ATC Ile								432
		130		•		•	135				,	140	•			-	
55	ממ	ጥ ልር	ממ	AGC	ר <u>א</u> ת.	אַאַר	ርጥሮ	ጥልጥ	ATC	ב) די ע	פרר	GDC	אסמ	ראה	מממ	אמר	480
									Ile								-200
		•															

								••							
	145				150				155				160		
5										ATC Ile				!	528
10										CCC Pro					576
										ACC Thr					624
15										GTC Val 220				. (672
20										GAG Glu				•	720
25										AGA Arg				•	768
20										ACA Thr					816
30										GGA Gly					864
35										AAT Asn 300					912
40										GCC Ala					960
45										AAA Lys				1	800
50				Phe						GAA Glu		Gln		1	056
50			Val				Asp			CTT Leu	Gln			. 1	104
55										CTT				1	152

		370					375					380					
	CTG	TGT	GGA	ATC	AAG	CAC	CTT	CAT	TCT	GCT	GGA	ATT	ATT	CAT	CGG	GAC	1200
	Leu	Cys	Gly	Ile	Lys	His	Leu	His	Ser	Ala	Gly	Ile	Ile	His	Arg	qaA	
5	385					390					395					400	
												TGC				_	1248
	Leu	гàг	Pro	ser	405	TTE	val	vaı	ьys	ser 410	Asp	Cys	Thr	Leu	ьуs 415	11e	
10					403					410					413		
	CTT	GAC	TTC	GGT	CTG	GCC	AGG	ACT	GCA	GGA	ACG	AGT	TTT	ATG	ATG	ACG	1296
	Leu	Asp	Phe	Gly	Leu	Ala	Arg	Thr	Ala	Gly	Thr	Ser	Phe	Met	Met	Thr	
				420					425					430			
45	com	m > m	CITI N	CTC	7) CT		ma c	m» a	202	aa s	000	CAC	C/II/C	אתמ	C TTTT	CCC	1244
15						•						GAG Glu				_	1344
	FIO	ı yı	435	, u		y	- 7 -	440	nr 9	ALU	110	014	445	,		017	
					*												
	ATG	GGC	TAC	AAG	GAA	AAC	GTG	GAT	TTA	TGG	TÇT	GTG	GGG	TGC	TTA	ATG	1392
20	Met	_	Tyr	Lys	Glu	Asn		Asp	Leu	Trp	Ser	Val	Gly	Cys	Ile	Met	
		450					455					460					
	GGA	GAA	ATG	GTT	TGC	CAC	AAA	ATC	CTC	TTT	CCA	GGA	AGG	GAC	TAT	ATT	1440
												Gly					
25	465					470					475					480	
												ACA Thr					1488
	Asp	GIII	IIÞ	ASII	485	Val	116	GIU	GIII	490	GIY	1111	PIO	Суб	495	GIU	
30					100					150							
	TTC	ATG	AAG	AAA	CTG	CAA	CCA	ACA	GTA	AGG	ACT	TAC	GTT	GAA	AAC	AGA	1536
	Phe	Met	Lys	-	Leu	Gln	Pro	Thr	Val	Arg	Thr	Tyr	Val.		Asn	Arg	
				500					505					510			
35	CCT	ααα	ייעדי	GCT	GGA	ידביד	AGC	ւեւներ	GAG	מממ	CTC	TTC	ССТ	GAT	GTC	СТТ	1584
00												Phe			-		
		•	515		-	-		520		•			525	_			
40												GCC			_		1632
40	Pne	530	Ата	Asp	ser	GIU	535	Asn	гуѕ	ьец	гÀг	Ala 540	ser	GIN	Ald	Arg	
		230					J J J					340					
	GAT	TTG	TTA	TCC	AAA	ATG	CTG	GTA	ATA	GAT	GCA	TCT	AAA	AGG	ATC	TCT	1680
	Asp	Leu	Leu	Ser	Lys	Met	Leu	Val	Ile	Asp	Ala	Ser	Lys	Arg	Ile	Ser	
45	545					550					555					560	
	OM3	C N III	(12.2	com	OMO.	C	a a a	000	ma a	3.000	7. 7. CT	CTC.	TCC	መለመ	CATE	COT	1728
												GTC Val					1720
	vai	vob	OIU	niu	565	0111	*****	110	- 7 -	570	ADII	741	1-1	- / -	575		
50															-		
												GAC					1776
	Ser	Glu	Ala		Ala	Pro	Pro	Pro	_	Ile	Pro	qaA	Lys		Leu	Asp	
				580					585					590			
55	GAA	AGG	GAA	CAC	ACA	ATA	GAA	GAG	TGG	ααα	GAA	TTG	ДΤД	TAT	AAG	GAA	1824
												Leu					
		_							•	-				-	-		

85

595 600 605 GTT ATG GAC TTG GAG GAG AGA ACC AAG AAT GGA GTT ATA CGG GGG CAG 1872 Val Met Asp Leu Glu Glu Arg Thr Lys Asn Gly Val Ile Arg Gly Gln 5 610 CCC TCT CCT TTA GCA CAG GTG CAG CAG TGA 1902 Pro Ser Pro Leu Ala Gln Val Gln Gln 10 (2) INFORMATION FOR SEQ ID NO:45: (i) SEQUENCE CHARACTERISTICS: 15 (A) LENGTH: 633 amino acids (B) TYPE: amino acid (C) STRANDEDNESS: single (D) TOPOLOGY: linear 20 (ii) MOLECULE TYPE: protein (v) FRAGMENT TYPE: internal (xi) SEQUENCE DESCRIPTION: SEQ ID NO:45: Met Val Ser Lys Gly Glu Glu Leu Phe Thr Gly Val Val Pro Ile Leu 25 10 Val Glu Leu Asp Gly Asp Val Asn Gly His Lys Phe Ser Val Ser Gly 25 Glu Gly Glu Gly Asp Ala Thr Tyr Gly Lys Leu Thr Leu Lys Phe Ile 30 Cys Thr Thr Gly Lys Leu Pro Val Pro Trp Pro Thr Leu Val Thr Thr Leu Thr Tyr Gly Val Gln Cys Phe Ser Arg Tyr Pro Asp His Met Lys 70 75 35 Gln His Asp Phe Phe Lys Ser Ala Met Pro Glu Gly Tyr Val Gln Glu 90 Arq Thr Ile Phe Phe Lys Asp Asp Gly Asn Tyr Lys Thr Arg Ala Glu 105 Val Lys Phe Glu Gly Asp Thr Leu Val Asn Arg Ile Glu Leu Lys Gly 40 120 Ile Asp Phe Lys Glu Asp Gly Asn Ile Leu Gly His Lys Leu Glu Tyr 135 Asn Tyr Asn Ser His Asn Val Tyr Ile Met Ala Asp Lys Gln Lys Asn 150 155 45 Gly Ile Lys Val Asn Phe Lys Ile Arg His Asn Ile Glu Asp Gly Ser 170 Val Gln Leu Ala Asp His Tyr Gln Gln Asn Thr Pro Ile Gly Asp Gly 185 Pro Val Leu Pro Asp Asn His Tyr Leu Ser Thr Gln Ser Ala Leu 50 200 Ser Lys Asp Pro Asn Glu Lys Arg Asp His Met Val Leu Leu Glu Phe 215 Val Thr Ala Ala Gly Ile Thr Leu Gly Met Asp Glu Leu Tyr Lys Ser 230 · 235 55 Gly Leu Arg Ser Arg Ala Arg Ala Ile Met Ser Arg Ser Lys Arg Asp

250

	Asn	Asn	Phe	Tyr 260	Ser	Val	Glu	Ile	Gly 265	Asp	Ser	Thr	Phe	Thr 270	Val	Leu
	Lys	Arg	Tyr 275	Gln	Asn	Leu	Lys	Pro 280	Ile	Gly	Ser	Gly	Ala 285	Gln	Gly	Ile
5	Val	Cys 290	Ala	Ala	Tyr	Asp	Ala 295	Ile	Leu	Glu	Arg	Asn 300	Val	Ala	Ile	Lys
	Lys 305	Leu	Ser	Arg	Pro	Phe	Gln	Asn	Gln	Thr	His 315	Ala	Lys	Arg	Ala	Tyr 320
10	Arg	Glu	Leu		Leu 325	Met	Lys	Cys	Val	Asn 330	His	Lys	Asn	Ile	Ile 335	Gly
	Leu		•	340					345					350		-
÷	Val	Tyr	11e 355	Val	Met	Glu	Leu	Met 360	Asp	Ala	Asn	Leu	Сув 365	Gln	Val	Ile
15	Gln	Met 370	Glu	Leu	Asp	His	Glu 375	Arg	Met	Ser	Tyr	Leu 380	Leu	Tyr	Gln	Met
	385	_	_			390					395			His		400
20		•			405				_	410	-	-		Leu	415	
		_		420					425					Met 430		
		-	435			_	-	440					445	Ile		
25		450	_	_			455			-		460		Cys		
	465				_	470	_				475	_		Asp		480
30	_				485					490				Cys	495	
				500					505					Glu 510		
		_	515		-			520					525	Asp		
35		530		_			535				•	540		Gln		
	545					550					555			Arg Tyr		560
40		_			565				-	570					575	
	Ser			580					585					590 Tyr		
15			595					600					605			
45		610		Leu			615			MSII	GIÀ	620	.116	Arg	GIY.	GIII
	625	Per	FIO	บะน		630	val	GIII	9111							

50 (2) INFORMATION FOR SEQ ID NO:46:

- (i) SEQUENCE CHARACTERISTICS:
 - (A) LENGTH: 1824 base pairs
 - (B) TYPE: nucleic acid
 - (C) STRANDEDNESS: single
 - (D) TOPOLOGY: linear

(ii)	MOLECULE	TYPE:	CDNA
1/			

(ix) FEATURE:

5 (A) NAME/KEY: Coding Sequence (B) LOCATION: 1...1821

(D) OTHER INFORMATION:

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:46:

		()	ci) S	EQUE	ENCE	DESC	RIPT	: NOI	SEC	ID	NO:4	6:				
10				AAG Lys												48
·	1				5					10			 	15		
15				GAC Asp 20												96
20				GGC Gly												144
25				GGC Gly												192
				GGC Gly												240
30				TTC Phe												288
35				TTC Phe 100												336
40				GAG Glu												384
45				AAG Lys												432
50				AGC Ser												480
30				GTG Val											Ser	528
55															GGC Gly	576

		180			185				190		
5	GTG Val										624
10	 AAA Lys 210										672
	 ACC Thr										720
15	 CTC Leu										768
20	CAG Gln										816
25	 CTG Leu									_	864
30	 GAC Asp 290										912
30	TTT Phe										960
35	CTT Leu										1008
40	ACA Thr										1056
45	CAT His										1104
-	ACA Thr 370							Ile		GGT	1152
50	Lys						Arg			CCT Pro 400	1200
55	AAT Asn									TTT	1248

					405					410					415			
5												GGC Gly					1296	
10												TGG Trp					1344	
												ATG Met 460					1392	
15												ATT Ile					1440	
20												GAG Glu					1488	
25												TCT Ser					1536	
20												GCC Ala					1584	
30												TCA Ser 540					1632	;
35												GCT Ala					1680	,
40	CCT Pro	GAT Asp	GAT Asp	GAA Glu	CCA Pro 565	GTG Val	GCC Ala	GAT Asp	CCT Pro	TAT Tyr 570	Asp	CAG Gln	TCC	TTT Phe	GAA Glu 575	AGC Ser	1728	3
45					Ile					Ser		ACC Thr			Glu		1776	5
50				Val					Asp			GAG		Glu		TGA	183	24

(2) INFORMATION FOR SEQ ID NO:47:

(i) SEQUENCE CHARACTERISTICS:

(A) LENGTH: 607 amino acids
(B) TYPE: amino acid

- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(v) FRAGMENT TYPE: internal

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:47:

10	Met 1	Val	Ser	Lys	Gly 5	Glu	Glu	Leu	Phe	Thr 10	Gly	Val	Val	Pro	Ile 15	Leu
				20		-		Asn	25					30		
:	Glu	Gly	Glu 35	Gly	Asp	Ala	Thr	Tyr 40	Gly	Lys	Leu	Thr	Leu 45	Lys	Phe	Ile
15	Сув	Thr 50	Thr	Gly	Lys	Leu	Pro 55	Val	Pro	Trp	Pro	Thr 60	Leu	Val	Thr	Thr
	65			_		70	-	Phe		_	75		_			80
20				٠.	85			Ala		90	•				95	
				100				Asp	105					110		
		-	115					Leu 120					125			
25		130					135	Asn	•			140				
	145	_				150		Tyr			155					160
30	_		_		165			Ile		170					175	
				180	_	•	-	Gln	185					190		
			195			-		200					205	,		Leu
35		210					215	Arg				220				
	225				_	230					235					Ser 240
40	-		_		245	-	,	Met		250					255	
				260					265					270		Gln
			275					280					285			Ala
45		290					295			•		300				Arg
	305			•		310					315					Arg 320
50					325					330					335	
	Phe	Thr	Pro	Ala 340		Ser	Leu	Glu	Glu 345		Asn	Asp	Val	Tyr 350		Val
	Thr	His	Leu 355	Met	Gly	Ala	Asp	Leu 360		Asn	Ile	Val	Lys 365		Gln	Lys
55	Leu	Thr 370	_	Asp	His	Val	Gln 375		Leu	Ile	Tyr	Gln 380		Leu	Arg	Gly

		Lys	Tyr	Ile	His		Ala	Asp	Ile	Ile		Arg	Asp	Leu	Lys		
	385	3	7	7 J -	*** 1	390	~ 1	7 ~~	C1 - C	~ 1	395	*	T1.	T	7	400	
					405			_	_	410		_			Asp 415		
5	Gly	Leu	Ala	Arg 420	His	Thr	Asp	Asp	Glu 425	Met	Thr	Gly	Tyr	Val 430	Ala	Thr	
•	Arg	Trp	Tyr 435	Arg	Ala	Pro	Glu	Ile 440	Met	Leu	Asn	Trp	Met 445	His	Tyr	Asn	
10	Gln	Thr 450	Val	Asp	Ile	Trp	Ser 455	Val	Gly	Сув	Ile	Met 460	Ala	Glu	Leu	Leu	
	Thr 465	Gly	Arg	Thr	Leu	Phe 470	Pro	Gly	Thr	Asp	His	Ile	Asp	Gln	Leu	Lys 480	
		Ile	Leu	Arg	Leu 485	Val	Gly	Thr	Pro	Gly 490	Ala	Glu	Leu	Leu	Lys 495	Lys .	
15	Ile	Ser	Ser	Glu 500		Ala	Arg	Asn	Tyr 505		Gln	Ser	Leu	Thr 510	Gln	Met	
	Pro	Lуз	Met 515		Phe	Ala	Asn	Val 520		Ile	Gly	Ala	Asn 525		Leu	Ala	
20	Val	Asp 530		Leu	Glu	Lys	Met 535		Val	Leu	Asp	Ser 540		Lys	Arg	Ile	
	Thr 545		Ala	Gln	Ala	Leu 550		His	Ala	Tyr	Phe 555		Gln	Tyr	His	Asp 560	
		Asp	Asp	Glu	Pro 565		Ala	Asp	Pro	Tyr 570		Gln	Ser	Phe	Glu 575		
25	Arg	Asp	Leu	Leu 580		Asp	Glu	Trp	Lys 585		Leu	Thr	Tyr	Asp 590	Glu	Val	
	Ile	Ser	Phe 595		Pro	Pro	Pro	Leu 600		Gln	Glu	Glu	Met 605	Glu	Ser		
30			(2) IN:	FORM	OITA	1 FO	R SE	Q ID	NO:	48:						٠
		(:	(A)	EQUE	GTH:	290	7 ba	se pa									
35			(C)	TYP: STR TOP	ANDEI	ONES	3: s:	ingl	e								
				MOLE FEAT		TYPI	E: cl	AND	•								
40		ν.			•												
			(B) NAI) LO) OTI	CATIO	ON: ∵	1:	2904	eque	nce			•				
45		(:	xi) :	SEQU	ENCE	DES	CRIP'	TION	: SE	Q ID	NO:	48:					
															ATC Ile 15		4.8
50															TCC Ser		96
55														AAG Lys	TTC Phe		144

. 92

		35			40				45				
5	ACC Thr 50											19	92
10	ACC Thr											24	10
	CAC His											28	88
15	ACC Thr												36
20	AAG Lys											31	84
25	GAC Asp 130											4:	32
20	TAC Tyr											4	80
30	ATC Ile											5	28
35	CAG Gln											5	76
40	GTG Val											6	24
45	AAA Lys 210	Asp							Leu			6	72
	ACC Thr							Glu				7	20
50	CTC Leu						Gln				Tyr	7	768
55											GAC Asp	8	816

_			260				265				270	х.		
5			GTG Val						Leu					864
			GCC Ala											912
10			GGG Gly											960
15			AAA Lys											1008
20			CCT Pro 340											1056
25			GCT Ala											1104
20		Ile	GCC Ala											1152
30			CTG Leu						Thr					1200
35			GAA Glu											1248
40			ATG Met 420	Ile				Leu				Lys	CGC	1296
45			Asp				Val				Val		AGT Ser	1344
50		Ile				Glu				Glu			ATT Ile	1392
50	Leu				Ile				Ile				TAT Tyr 480	1440
55													CAA Gln	1488

								94						
				485				490				495		
5			AAA Lys 500											1536
10			CTT Leu										GAA Glu	1584
			AAA Lys											1632
15			GCA Ala											1680
20			AAC Asn											1728
25			GGA Gly 580											1776
20			GAC Asp											1824
30			TAT Tyr							Asn			TTA Leu	1872
35													TTA Leu 640	1920
40			TCT Ser											1968
45			TAT Tyr 660										GTA Val	2016
							Val				Ile		GCT Ala	2064
50		Lys				Tyr				Gln			AGT Ser	2112
55													GAA Glu	2160

										30							•
	705					710					715					720	
5	ATC Ile	CAA Gln	ATG Met	AAA Lys	AGG Arg 725	ACA Thr	GCT Ala	ATT Ile	GAA Glu	GCA Ala 730	TTT Phe	AAT Asn	GAA Glu	ACC Thr	ATA Ile 735	AAA Lys	2208
	ATA Ile	TTT Phe	GAA Glu	GAA Glu 740	CAG Gln	TGC Cys	CAG Gln	ACC Thr	CAA Gln 745	GAG Glu	CGG Arg	TAC Tyr	AGC Ser	AAA Lys 750	GAA Glu	TAC Tyr	2256
10	ATA Ile	GAA Glu	AAG Lys 755	TTT Phe	AAA Lys	CGT Arg	GAA Glu	GGC Gly 760	AAT Asn	GAG Glu	AAA Lys	GAA Glu	ATA Ile 765	CAA Gln	AGG Arg	ATT Ile	2304
15	ATG Met	CAT His 770	AAT Asn	TAT Tyr	GAT Asp	AAG Lys	TTG Leu 775	AAG Lys	TCT Ser	CGA Arg	ATC Ile	AGT Ser 780	GAA Glu	ATT Ile	ATT Ile	GAC Asp	2352
20	AGT Ser 785	AGA Arg	AGA Arg	AGA Arg	TTG Leu	GAA Glu 790	GAA Glu	GAC Asp	TTG Leu	AAG Lys	AAG Lys 795	CAG Gln	GCA Ala	GCT Ala	GAĞ Glu	TAT Tyr 800	2400
25	CGA Arg	GAA Glu	ATT Ile	GAC Asp	AAA Lys 805	CGT	ATG Met	AAC Asn	AGC Ser	ATT Ile 810	AAA Lys	CCA Pro	GAC Asp	CTT	ATC Ile 815	Gln	2448
	CTG Leu	AGA Arg	AAG Lys	ACG Thr 820	AGA Arg	GAC Asp	CAA Gln	TAC Tyr	TTG Leu 825	ATG Met	TGG Trp	TTG Leu	ACT	CAA Gln 830	AAA Lys	GGT Gly	2496
30	GTT Val	CGG	CAA Gln 835	AAG Lys	AAG Lys	TTG Leu	AAC Asn	GAG Glu 840	Ţrp	TTG Leu	GGC Gly	AAT Asn	GAA Glu 845	AAC Asn	ACT Thr	GAA Glu	2544
35	GAC Asp	CAA Gln 850	Tyr	TCA Ser	CTG Leu	GTG Val	GAA Glu 855	Asp	GAT Asp	GAA Glu	GAT Asp	TTG Leu 860	Pro	CAT His	CAT His	GAT Asp	2592
40	GAG Glu 865	Lys	ACA Thr	TGG	AAT Asn	GTT Val 870	Gly	AGC Ser	AGC Ser	AAC	CGA Arg 875	, Asn	: AAA Lys	GCT Ala	GAA	A AAC A Asn 880	2640
45	CTG Leu	TTG Leu	CGA Arg	GGG Gly	AAG Lys 885	Arg	GAI Asp	GGC Gly	C ACT	TTI Phe	Lei	T GTC	CGG Arg	GAG Glu	8 AG0 8 Se1	C AGT r Ser	2688
	AAA Lys	CAG Glr	GGC Gly	TGC Cys	Tyr	GCC Ala	TGC Cys	TC1	r GTA c Val 905	. Val	GT(GAC L Asp	GGC Gly	GAA Glu 910	ı Val	A AAG l Lys	2736
50	CAT His	TGI Cys	r GTC Val 915	. Ile	AAC Asr	: AAA	A ACI	A GC C Ala 920	a Thi	GG(TA'	r GG(r Gly	7 TT 7 Phe 925	e Ala	C GAG	G CCC u Pro	2784
55	ТАТ Туз	C AAC	TTC Lev	TAC	AGC Sei	TCT Sei	CTC	B AA	A GA/ s Glu	CTO	G GTO	G CTI	A CA'	TAC Ty:	C CA	A CAC n His	2832

935 940 930 ACC TCC CTT GTG CAG CAC AAC GAC TCC CTC AAT GTC ACA CTA GCC TAC 2880 Thr Ser Leu Val Gln His Asn Asp Ser Leu Asn Val Thr Leu Ala Tyr 5 950 2907 CCA GTA TAT GCA CAG CAG AGG CGA TGA Pro Val Tyr Ala Gln Gln Arg Arg 10 (2) INFORMATION FOR SEQ ID NO:49: (i) SEQUENCE CHARACTERISTICS: (A) LENGTH: 968 amino acids 15 (B) TYPE: amino acid (C) STRANDEDNESS: single (D) TOPOLOGY: linear (ii) MOLECULE TYPE: protein 20 (v) FRAGMENT TYPE: internal (xi) SEQUENCE DESCRIPTION: SEQ ID NO:49: Met Val Ser Lys Gly Glu Glu Leu Phe Thr Gly Val Val Pro Ile Leu 25 Val Glu Leu Asp Gly Asp Val Asn Gly His Lys Phe Ser Val Ser Gly Glu Gly Glu Gly Asp Ala Thr Tyr Gly Lys Leu Thr Leu Lys Phe Ile 30 Cys Thr Thr Gly Lys Leu Pro Val Pro Trp Pro Thr Leu Val Thr Thr Leu Thr Tyr Gly Val Gln Cys Phe Ser Arg Tyr Pro Asp His Met Lys 75 Gln His Asp Phe Phe Lys Ser Ala Met Pro Glu Gly Tyr Val Gln Glu 35 Arg Thr Ile Phe Phe Lys Asp Asp Gly Asn Tyr Lys Thr Arg Ala Glu 105 Val Lys Phe Glu Gly Asp Thr Leu Val Asn Arg Ile Glu Leu Lys Gly 120 40 Ile Asp Phe Lys Glu Asp Gly Asn Ile Leu Gly His Lys Leu Glu Tyr 135 Asn Tyr Asn Ser His Asn Val Tyr Ile Met Ala Asp Lys Gln Lys Asn 155 Gly Ile Lys Val Asn Phe Lys Ile Arg His Asn Ile Glu Asp Gly Ser 45 170 Val Gln Leu Ala Asp His Tyr Gln Gln Asn Thr Pro Ile Gly Asp Gly 185 Pro Val Leu Leu Pro Asp Asn His Tyr Leu Ser Thr Gln Ser Ala Leu 200 50 Ser Lys Asp Pro Asn Glu Lys Arg Asp His Met Val Leu Leu Glu Phe Val Thr Ala Ala Gly Ile Thr Leu Gly Met Asp Glu Leu Tyr Lys Ser 235 230 Gly Leu Arg Ser Met Ser Ala Glu Gly Tyr Gln Tyr Arg Ala Leu Tyr

	Asp	Tyr	Lys	Lys 260	Glu	Arg	Glu	Glu	Asp 265	Ile	Asp	Leu	His	Leu 270	Gly	Asp
	Ile	Leu	Thr 275		Asn	Lys	Gly	Ser 280		Val	Ala	Leu	Gly 285	Phe	Ser	Asp
5	Gly	Gln 290	Glu	Ala	Arg	Pro	Glu 295	Glu	Ile	Gly	Trp	Leu 300	Asn	Gly	Tyr	Asn
	Glu 305	Thr	Thr	Gly	Glu	Arg 310	Gly	Asp	Phe	Pro	Gly 315	Thr	Tyr	Val	Glu	Tyr 320
10					325					330.				Arg	335	•
	Arg	Pro	Leu	Pro 340	Val.	Ala	Pro	Gly	Ser 345	Ser	Lys	Thr	Glu	Ala 350	Asp	Val
			355					360	_				365	Phe		
15		370					375					380		Ala		
	385					390					395			Ser		400
20					405					410				Pro	415	
	. •			420					425					Phe 430		
,	•		435					440					445	Val		
25		450	•				455					460		Glu		
	465			_	-	470		-			475			His		480
30	_				485					490				Leu	495	
				500					505					Glu 510		
			515					520					525			
35		530					535					540		Trp		
	545					550					555			Pro		560
40					565					570				Asn	575	
	_	_		580	_				585					Lys 590		
	_		595				•	600			-		605			
45		610					615					620		Asn		
	625	-				630	_	_	-	_	635			Asp		64
50					645					650		·		Asn	655	
				660					665					Tyr 670		
		_	675					680					685			
55	Val	Gly	ГÀЗ	Lys	Leu	His	Glu	Tyr	Asn	Thr	Gln	Phe	Gln	Glu	гуs	se

	Arg	Glu	Tyr	Asp	Arg	Leu	Tyr	Glu	Glu	Tyr		Arg	Thr	Ser	Gln		
	705					710		_,	~3	• • •	715		~ 3	ml	T1.	720	
					725					730		Asn			735		
5	Ile	Phe	Glu	Glu 740	Gln	Сув	Gln	Thr	Gln 745	Glu	Arg	Tyr	Ser	Lys 750	Glu	Tyr	
	Ile	Glu	Lys 755	Phe	Lys	Arg	Glu	Gly 760	Asn	Glu	Lys	Glu	Ile 765	Gln	Arg	Ile	
10	Met	His		Tyr	Asp	Lys	Leu 775	Lys	Ser	Arg	Ile	Ser 780		Ile	Ile	Asp	
10	.Ser		Arg	Arg	Leu	Glu 790	Glu	Asp	Leu	ŗàs	Lys 795	Gln	Ala	Ala	Glu	Tyr 800	
	Arg	Glu	Ile	Asp	Lys 805		Met	Asn	Ser	Ile 810	Lys	Pro	Asp	Leu	Ile 815	Gln	
15	Leu	Arg	Lys	Thr 820		Asp	Gln	Tyr	Leu 825		Trp	Leu	Thr	Gln 830	Lys	Gly	
	Val	Arg	Gln 835		Lys	Leu	Asn	Glu 840	Trp	Leu	Gly	Asn	Glu 845			Glu	
20	Авр		Tyr	Ser	Leu	Val	Glu 855	Asp		Glu	Asp	Leu 860		His	His	Asp	
20		-	Thr	Trp	Asn	Val 870	Gly		Ser	Asn	Arg 875	Asn	Lys	Ala	Glu	Asn 880	
	865 Leu	Leu	Arg	Gly		Arg		Gly	Thr	Phe 890			Arg	Glu	Ser 895	Ser	
25	Lys	Gln	Gly				Cys	Ser	Val 905	Val	Val	Asp	Gly	Glu 910	Val	Lys	• . •
	His	Cha				Lys	Thr		Thr		Tyr	Gly	Phe 925	Ala		Pro	
	Tyr				Ser	Ser				Leu	Val	Leu 940	His		Gln	His	
30				Val	Gln				Ser	Leu		Val		Lev	Ala	Tyr 960	•
	945 Pro		Tyr	Ala				Arg	Ţ		955	•		•		300	
35					965		50				50						
										NO:	50:						
		((A)	EQUE	GTH:	216	0 ba	se p									
40			(C)	TYP STR TOP	ANDE	DNES	SS: S	ingl	le								
r				MOLE											•		
45				FEAT												•	
			(E	A) NA B) LO O) OT	CATI	ON:	i	.215	7	ence							
50			(xi)	SEQU	JENCI	E DES	SCRII	PTIO	N: S	EQ II	ои о	:50:					
																C CTG e Leu	
55	Met	. va.	ı sei	с гу	5 5	י פדו	u GT!	ת הפי	u Pili	10	. 31	y va.	_ va	_ FL	15		

							33							
	GAG Glu												96	
5	GGC Gly												144	
10	ACC Thr 50												192	
15	ACC Thr											AAG Lys 80	240	
	CAC His												288	
20	ACC Thr												336	
25	AAG Lys												384	
30	GAC Asp 130												432	
35	TAC Tyr												480	
40	ATC Ile											Ser	528	
40											Asp	GGC	576	
45		Leu				Tyr				Ser		CTG Leu	624	
50					Arg				Leu			TTC Phe	672	
55	Thr			Thr				Glu				S TCC S Ser 240	720	

						100					
	CTC Leu								_		768
5	 CCA Pro	 		-			 	 			816
10	GCT Ala										864
15	GAA Glu 290									-	912
20	 AAA Lys										960
20	 TGT Cys				-						1008
25	GGA Gly										1056
30	 TAC Tyr								_		1104
35	TCC Ser 370										1152
	TGG Trp										1200
40	GAA Glu							Val			1248
45	CAC His										1296
50	CGA Arg										1344
55									CCA Pro		1392

						101					
	AGT Ser										1440
5	GGA Gly										1488
10	CCA Pro								_	•	1536
15	GAT Asp									TCA Ser	1584
	GCA Ala 530										1632
20	CAG Gln										1680
25	AGG Arg										1728
30	GAA Glu										1776
35	GGT Gly										1824
40	CAG Gln 610	Ser									1872
40	TGT Cys										1920
45	TTT Phe										1968
50	 TAT										2016
55	TGG Trp										2064

102

										102							
		ATT Ile 690														GTA Val	2112
5		ACT Thr									•					TAA	2160
10			(2)	INI	FORM	OITA	V FOI	R SE(Q ID	NO:5	51:						
÷		i)	(A)		GTH:	719	amiı	RISTI no ac		•							
15			(C)		ANDEI	ONES	3: s:	ingle	e								
20							_	rote: terna									
	•	(2	ci) S	SEQUI	ENCE	DES	CRIP'	rion	: SE	מו כ	NO:	51:				*	
	Met 1	Val	Ser	Lys	Gly 5	Glu	Glu	Leu	Phe	Thr 10	Gly	Val	Val	Pro	Ile 15	Leu	
25	Val	Glu	Leu	Asp 20	Gly	Asp	Val	Asn	Gly 25	His	Lys	Phe	Ser	Val 30	Ser	Gly	•
	Glu	Gly	Glu 35	Gly	Asp	Ala	Thr	Tyr 40	Gly	Lys	Leu	Thr	Leu 45	ГЛЗ	Phe	Ile	
30	Cys	Thr 50	Thr	Gly	Lys	Leu	Pro 55	Val	Pro	Trp	Pro	Thr 60	Leu	Val	Thr	Thr	
	Leu 65	Thr	Tyr	Gly	Val	Gln 70	Сув	Phe	Ser	Arg	Tyr 75	Pro	Asp	His	Met	Lys 80	
	Gln	His	Asp	Phe	Phe 85	Lys	Ser	Ala	Met	Pro 90	Glu	Gly	Tyr	Val	Gln 95	Glu	
35	_	Thr		100					105					110		-	
		Lys	115					120					125				
40		Asp 130					135				•	140					
	Asn 145	-				150		_			155					160	
		Ile	_		165					170					175		
45				180	_		-		185					190		Gly	
			195				•	200					205			Leu	
50		210					215					220				Phe	
	Val 225	Thr	Ala	Ala	Gly	Ile 230	Thr	Leu	Gly	Met	Asp 235		Leu	Tyr	. r.\a	Ser 240	
	Gly	Leu	Arg	Ser	Arg 245	Ala	Gln	Ala	Ser	Asn 250		Thr	Met	Ser	Ser 255	Ile	
	_		-1		D	-		7	-	•	T	T	~ 1		T	T	

Leu Pro Phe Thr Pro Pro Val Val Lys Arg Leu Leu Gly Trp Lys Lys

	Ser	Ala	Gly 275	Gly	Ser	Gly	Gly	Ala 280	Gly	Gly	Gly	Glu	Gln 285	Asn	Gly	Gln
	Glu	Glu 290	Lys	Trp	Cys	Glu	Lys 295	Ala	Val	Lys	Ser	Leu 300	Val	Lys	Lys	Leu
5	Lys 305	Lys	Thr	Gly	Arg	Leu 310	Asp	Glu	Leu	Glu	Lys 315	Ala	Ile	Thr	Thr	Gln 320
		_			325					330			_		.335	
10				340					345					Thr 350		
		-	355					360	_			_	365	Arg		
		370				_	375					380		Arg		_
15	385	_				390					395	_		Ile		400
	_				405			_	_	410			_	Val	415	
20	_			420					425					Val 430		
		-	435			•		440					445	Asp		
		450					455					460		Ile		•
25	465					470					475	_	_	Ile		480
		_			485	_				490			•	qaA	495	
30				500					505					Asn 510		
			515					520					525	Trp		
35		530					535				_	540		Phe		
33	545					550					555			Asn		560
					565	•				570				Leu	575	
40				580					585					590 Ala		
			595					600					605	Pro		
45		610					615		_			620		Asn		
,	625					630		•			635			Phe		640
					645					650				Phe	655	
50			•	660					665					670 Thr		
			675					680					685	Asp		
55	_	690					695	_				700		Met		
JJ	705	1111	GIII	MEC	GIY	710	FIO	Ser	val	wid	715	PCI	Set	MCC.	261	

			(2) IN	FORM	ATIO	N FO	R SE	QID	NO:	52:					·	
5		((A) (B) (C)	LEN TYP STR	NCE (GTH: E: ni ANDEI	242; ucle: DNES	l basic as	se pa cid ingle	airs					·			
10				MOLE FEAT	CULE URE:	TYP	E: cl	DNA		•					•		
15	:	· .	(B (D) LO	ME/KI CATION HER I	ON:	RMAT	2418 ION:			NO	: 2 .					
,	3 DC												 				
20														ATC Ile 15			48
25														TCC Ser			96
														TTC Phe			144
30														ACC Thr			192
35														ATG Met			240
40														CAG Gln 95			288
45														GCC Ala			336
50														AAG Lys			384
														GAG Glu			432
55														AAG Lys			480

												•
	145			150			155			160		
5			GTG Val						Asp			528
10			GCC Ala 180									576
10			CTG Leu					_				624
15			CCC Pro			-						672
20			GCC Ala									720
25			TCT Ser								•	768
30			ATT Ile 260									816
. 00			AGT Ser			•				ACA Thr		864
35			AGA Arg							AAA Lys		912
40			TTG Leu									960
45			AAA Lys								:	1008
50			GGT Gly 340							CTC Leu	. :	1056
50										TAT	8 8	1104
55										CCA Pro		1152

106

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		370			375			380			٠
5									CTC Leu		1200
10									AAG Lys		1248
	GTG Val								GAA Glu		1296
15									TCG Ser 445		1344
20									AAT Asn		1392
25									AGT Ser		1440
20									CAG Gln		1488
30									GGT Gly		1536
35									AGT Ser 525		1584
40									CAT His		1632
45									CCT Pro		1680
50									GCT Ala		1728
									GTA Val		1776
55									GAT Asp		1824

												•	
		595				60,0			605				
5			_							TCC Ser		1872	2
										GGC Gly		1920)
										AGG Arg		1968	3
15				Val						AGA Arg 670		2016	5
20										AGT Ser		2064	1
25								 		CAG Gln		211:	2
30										GCC Ala		216	כ
										CCA Pro		220	В
35										CGT Arg 750		225	5
40										GAT Asp		230	4
45										CAC His		235	2
50										CCG Pro		240	0
				TTA Leu 805	TGA							24	21

(2) INFORMATION FOR SEQ ID NO:53:

WO 98/45704 PCT/DK98/00145

108

```
(i) SEQUENCE CHARACTERISTICS:
              (A) LENGTH: 806 amino acids
              (B) TYPE: amino acid
 5
              (C) STRANDEDNESS: single
              (D) TOPOLOGY: linear
            (ii) MOLECULE TYPE: protein
            (v) FRAGMENT TYPE: internal
10
            (xi) SEQUENCE DESCRIPTION: SEQ ID NO:53:
      Met Val Ser Lys Gly Glu Glu Leu Phe Thr Gly Val Val Pro Ile Leu
15
      Val Glu Leu Asp Gly Asp Val Asn Gly His Lys Phe Ser Val Ser Gly
                                      25
      Glu Gly Glu Gly Asp Ala Thr Tyr Gly Lys Leu Thr Leu Lys Phe Ile
      Cys Thr Thr Gly Lys Leu Pro Val Pro Trp Pro Thr Leu Val Thr Thr
20
      Leu Thr Tyr Gly Val Gln Cys Phe Ser Arg Tyr Pro Asp His Met Lys
                          70
      Gln His Asp Phe Phe Lys Ser Ala Met Pro Glu Gly Tyr Val Gln Glu
                      85
                                          90
25
      Arg Thr Ile Phe Phe Lys Asp Asp Gly Asn Tyr Lys Thr Arg Ala Glu
                  100
                                      105
      Val Lys Phe Glu Gly Asp Thr Leu Val Asn Arg Ile Glu Leu Lys Gly
                                  120
      Ile Asp Phe Lys Glu Asp Cly Asn Ile Leu Cly His Lys Leu Glu Tyr
30
                              135
      Asn Tyr Asn Ser His Asn Val Tyr Ile Met Ala Asp Lys Gln Lys Asn
                          150
                                              155
      Gly Ile Lys Val Asn Phe Lys Ile Arg His Asn Ile Glu Asp Gly Ser
                                          170
35
      Val Gln Leu Ala Asp His Tyr Gln Gln Asn Thr Pro Ile Gly Asp Gly
                                      185
      Pro Val Leu Leu Pro Asp Asn His Tyr Leu Ser Thr Gln Ser Ala Leu
                                  200
      Ser Lys Asp Pro Asn Glu Lys Arg Asp His Met Val Leu Leu Glu Phe
40
                              215
                                                   220
      Val Thr Ala Ala Gly Ile Thr Leu Gly Met Asp Glu Leu Tyr Lys Ser
                          230
                                              235
      Gly Leu Arg Ser Arg Ala Gln Ala Ser Asn Ser Asn Ser Thr Met Asp
                      245
                                          250
45
      Asn Met Ser Ile Thr Asn Thr Pro Thr Ser Asn Asp Ala Cys Leu Ser
                                      265
      Ile Val His Ser Leu Met Cys His Arg Gln Gly Glu Ser Glu Thr
              275
                                  280
      Phe Ala Lys Arg Ala Ile Glu Ser Leu Val Lys Lys Leu Lys Glu Lys
50
                              295
      Lys Asp Glu Leu Asp Ser Leu Ile Thr Ala Ile Thr Thr Asn Gly Ala
                          310
                                               315
      His Pro Ser Lys Cys Val Thr Ile Gln Arg Thr Leu Asp Gly Arg Leu
```

Gln Val Ala Gly Arg Lys Gly Phe Pro His Val Ile Tyr Ala Arg Leu 340 345 350

330

325

	Trp	Arg	Trp 355	Pro	Asp	Leu	His	Lys 360	Asn	Glu	Leu	Lys	His 365	Val	Lys	Туг
	Сув	Gln 370	Tyr	Ala	Phe	Asp	Leu 375	Lys	Cys	Asp	Ser	Val 380	Cys	Val	Asn	Pro
5	Tyr 385	His	Tyr	Glu	Arg	Val 390	Val	Ser	Pro	Gly	Ile 395	Asp	Leu	Ser	Gly	Le:
	Thr	Leu	Gln	Ser	Asn 405	Ala	Pro	Ser	Ser	Met 410	Met	Val	Lys	Asp	Glu 415	Туг
10		His		420		_			425					430		
		Gln	435					440			_		445			
		Ser 450					455					460				
15	465	Ala				470					47.5					480
		Ile		_	485					490		•			495	
20		Pro		500					505					510		
		Tyr	515					520		_			525	•		
05		Tyr 530					535					540				
25	545	Pro				550					555	_				560
		Leu			565					570					575	-
30	_	Cys		580	٠.		٠		585	_				590		
		Lys	595				•	600					605			
35	_	610 Arg		_	-		615	4	_		_	620				
33	625	Gln				630		_		_	635			_	_	64
		Asp			645				_	650		_		_	655	
40		Arg		660					665					670		
		Lys	675					680		_		_	685			
45		690 Ala			_		695		_		_	700				
	705	Asn				710					715					72
		Leu			725					730	_			•	735	
50		Ile		740					745					750		
		Gln	755					760	_	_			765			
55		770 Ala					775		_	_		780				
55	785		ي ت	-141		790		O_LU	val	nen	705		FIEL	FIO	116	80

Asp Pro Gln Pro Leu Asp 805

5			(2)	INF	ORMA	TION	FOR	SEC	ID	NO : 5	4:						
		(i	(A)	LENG	TH:	3120	bas	e pa							•		
				TYPE					:								
10				TOPO				-									
		•		OLEC		TYPE	: cI	NA		•	•						
15				MAK				_	quer	ice							
				LOC													
		(x	ci) S	EQUE	ENCE	DESC	RIPI	CION:	SEC	Q ID	NO : 5	54:					
20	ΔΤС	GTG	AGC	DAG	GGC	GAG	GAG	CTG	TTC	ACC	GGG	GTG	GTG	CCC	ATC	CTG	. 48
	Met				Gly					Thr				Pro	Ile		
	1				5					10					15		
25														GTG			96
	Val	Glu	Leu	Asp 20	G1A	Asp	Val	Asn	G1y 25	·Hls	гув	Pne	ser	Val 30	ser	GIY	
	GAG	GGC	GAG	GGC	GAT	GCC	ACC	TAC	GGC	AAG	CTG	ACC	CTG	AAG	TTC	ATC	144
30			Glu											Lys			
			35														
														GTG Val			192
35	Сув	50	1111.	GIY	пур	neu	55	Vai	110	111	110	60	Dou	, , ,			
	CTG	ACC	TAC	GGC	GTG	CAG	TGC	TTC	AGC	CGC	TAC	CCC	GAC	CAC	ATG	AAG	240
•	Leu					Gln					Tyr			His			
40	65					70					75					80	
														GTC Val			288
	Gin	HIS	Авр	Pne	85	гув	Ser	Ala	Met	90	GIU	GIY	IYL		95	O1u	
45	CGC	ACC	ATC	TTC	TTC	AAG	GAC	GAC	GGC	AAC	TAC	AAG	ACC	CGC	GCC	GAG	336
				Phe					Gly					Arg		Glu	
				100					105					110			
50																GGC	384
50	val	тув	115	GIU	GIY	Asp	IIIL	120	val	VDII	vra	116	125		~ _J 5	Gly	
	ATC	GAC	TTC	AAG	GAG	GAC	GGC	AAC	ATC	CTG	GGG	CAC	AAG	CTG	GAG	TAC	432
		Asp					Gly	Asn				His	Lys			Tyr	
55		130					135					140					

																		•
		TAC Tyr																480
	145	ıyı	MSII	261	nis	150	Val	TYL		Met	155	Asp	БУБ	GIII	Був	160	•	
5		ATC																528
	Gly	Ile	ГÀЗ	Val.	165	Pne	гуs	He	Arg	170	Asn	ile	GIu	Asp	175	Ser		
10		CAG																576
	Val	Gln	Dea	180	web	ure	IYI	GIII	185	ASII		PIO	116	190	Asp	GIY		
		GTG Val														CTG		624
15	PIO.		195		110	кор		200	171	Deu	JCI	1111	205	DCI	1	Deu		
		AAA Lys																672
20	SCF	210	мър	110	ADII	014	215	rrg	nop	1113	nec	220	Deu	Dea	- Cau			
		ACC																720
	Val 225	Thr	Ala	Ala	Gly	11e 230	Thr	Leu	Gly	Met	Asp 235	Glu	Leu	Tyr	Lys	Ser 240	•	
25		CTC																768
	GIY	Leu	Arg	ser	245	Met	Ата	GIÀ	Trp	250	GIN	Ala	GIN	GIN	255	GIN		
30		GAC Asp																816
50	GIY	Asp	AIG	260	Arg	GIII	·	GIII	265	Бец		GIY	GIII	270	FIIC	110		
		GAG Glu														TGG		864
35			275			-		280		-			285					
																CAG Gln		912
40		290					295			1.05		300						
		CTG																960
	Leu 305	Leu	Glu	Gly	Leu	Val 310	Gln	Glu	Leu	Gln	Lys 315	Lys	Ala	Glu	His	Gln 320		
45		GGG																1008
	Val	Gly	Glu	Asp	Gly 325	Phe	Leu	Leu	Lys	11e 330	Lys	Leu	GIA	His	Tyr 335	Ala		
50																CGC		1056
50	ınr	GIN	ьeu	340		Inr	ıyr	Asp	Arg 345	cys	PTO	ьeu	GIU	350		Arg		
																GCC		1104
55	-ys	116	355	****		⊒ eu	- Y L	360	GIU	2111	w. A	u e u	365	_				

	AAT Asn 370									1152
5	CAC His			Gln						1200
10	GAC Asp									1248
15	ATC Ile									1296
20	CTG Leu								•	1344
	CAG Gln 450									1392
25	ACA Thr									1440
30	 CTG Leu									1488
35	ATC Ile									1536
40	GAG Glu									1584
40	ATC Ile 530									1632
45	CAG									1680
50	 AAC Asn	 	 		 	 Ala			Thr	1728
55	ATC Ile							Thr	AAG Lys	1776

														•
	 						GTG Val					_	_	1824
5	 	 		-			ACC Thr							1872
10	 	 					ACC Thr						•	1920
15							GAG Glu						ACC . Thr	1968
			TTC				TCA Ser 665	CTG		,				2016
20		GGT					ACA Thr					_		2064
25							AGC Ser							2112
30							GTC Val					_		2160
35							TGG Trp							2208
	 						GAC Asp 745							2256
40							AAG Lys							2304
45						Val	TTC Phe				Lys		AAC	2352
50	Ser		His		Glu					Leu			TGG Trp	2400
55				Glu					Trp				TGG Trp	2448

								117						
			GAC Asp 820											2496
5			GAT Asp										-	2544
10 ⁻			CTC Leu											2592
15			GAA Glu	Ile										2640
			AAC Asn											2688
20			TCC Ser 900											2736
25			CCT Pro											2784
30			CTG Leu											2832
35			GTC Val											2880
40			ACG Thr								Ala			2928
40			TAT Tyr 980											2976
45			GAA Glu			Leu				Asp				3024
50	Val		CTC Leu		Arg				Ser					3072
55			GCC Ala	Gly				Ala				Ser	TGA 1	3120

(2) INFORMATION FOR SEQ ID NO:55:

- (i) SEQUENCE CHARACTERISTICS:
 - (A) LENGTH: 1039 amino acids
 - (B) TYPE: amino acid
 - (C) STRANDEDNESS: single
 - (D) TOPOLOGY: linear
- 10 (ii) MOLECULE TYPE: protein

5

(v) FRAGMENT TYPE: internal

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:55:

					•											
15	Met	Val	Ser	Lys	Gly 5	Glu	Glu	Leu	Phe	Thr 10	Gly	Val	Val	Pro	Ile 15	Leu
				20	-	_			25		-			Val 30		
20	Glu	Gly	Glu 35	Gly	Asp	Ala	Thr	Tyr 40	Gly	Lys	Leu	Thr	Leu 45	Lys	Phe	Ile
	Cys	Thr 50	Thr	Gly	Lys	Leu	Pro 55	Val	Pro	Trp	Pro	Thr 60	Leu	Val	Thr	Thr
	Leu 65	Thr	Tyr	Gly	Val	Gln 70	Cys	Phe	Ser	Arg	Tyr 75	Pro	Asp	His	Met	Lys 80
25	Gln	His	Asp	Phe	Phe 85	Lys	Ser	Ala	Met	Pro 90	Glu	Gly	Tyr	Val	Gln 95	Glu
	Arg	Thr	Ile	Phe 100	Phe	Lys	Asp	Asp	Gly 105	Asn	Tyr	Lys	Thr	Arg 110	Ala	Glu
30	Val	Lys	Phe 115	Glu	Gly	Asp	Thr	Leu 120	Val	Asn	Arg	Ile	Glu 125	Leu	Lys	Gly
	Ile	Asp 130	Phe	Lys	Glu	Asp	Gly 135	Asn	Ile	Leu	Gly	His 140	Lys	Leu	Glu	Tyr
	Asn 145	Tyr	Asn	Ser	His	Asn 150	Val	Tyr	Ile	Met	Ala 155	Asp	Lys	Gln	Lys	Asn 160
35	-		_		165		-			170				Asp	175	
				180					185					Gly 190		
40			195					200	_				205	Ser		
		210					215					220		Leu		
	225				_	230			_	٠	235			Tyr		240
45					245					250				Gln	255	
	_			260					265		-			His 270		
50			275					280					285	Gln		
		290				_	295			_		300		Ala		
	Leu 305	Leu	Glu	Gly	Leu	Val 310	Gln	Glu	Leu	Gln	Lys 315	Lys	Ala	Glu	His	Gln 320
55	Val	Gly	Glu	Asp	Gly 325	Phe	Leu	Leu	Lys	Ile 330	Lys	Leu	Gly	His	Tyr 335	Ala

	Thr	Gln	Leu	Gln 340	Lys	Thr	Tyr	Asp	Arg 345	Cys	Pro	Leu	Glu	Leu 350		Arg
			355					360					365	Arg		
5		370					375					380		Met		
•	385					390					395			Leu		400
10					405					410				Gln	415	
	Phe			420					425					430		
			435					440					445	Glu		
15		450					455					460		Arg		
	465					470					475		-	His		480
20					485					490	•			qaA	495	
				500					505					Gly 510		
			515					520					525	Lys		
25		530					535					540		Glu		
	545					550		_			555			Leu		560
30					565					570				Thr	575	
				580					585					Gln 590		
25			595					600		_	_		605	Asn		
35		610					615					620		Gln		
	625					630				_	635		_	Ser	_	640
40					645					650				Thr	655	
				660					665					Lys 670		
45			675					680				_	685	Thr		
45		690					695	_				700		Phe		
	705					710			•		715			Ser		720
50					725				_	730				Ala -	735	
				740					745					Pro 750		
EE			755					760	_				765	Ser		
55	GIÀ	170	Tnr	тув	GIU	Asn	Leu 775	Val	Phe	Leu	Ala	780	гÀг	Leu	Phe	ASI

WO 98/45704 PCT/DK98/00145

		Ser	Ser	Ser	His		Glu	Asp	Tyr	Ser	_	Leu	Ser	Val	Ser				
	785 Com	~1 _~	Dho	A a m	7 ~~	790	7.00	T 011	Dwa	~1	795	200	т	mb ~	Phe	800			
	ser	GIII	Pile .	ASII	805	GIU	ASII	Leu	PIO	810	тр	ASII	ıyı	int	815	IIÞ			
5	Gln	Trp	Phe	Asp		۷al	Met	Glu	Val		Lvs	Lvs	His	His	Lys	Pro			
		•		820	•				825			•		830					
	His	Trp	Asn 835	Asp	Gly	Ala	Ile	Leu 840	Gly	Phe	Val	Asn	Lys 845	Gln	Gln	Ala			
	His	Asp	Leu	Leu	Ile	Asn	Lys	Pro	Asp	Gly	Thr	Phe	Leu	Leu	Arg	Phe			
10		850					855					860	•						
•		Asp	Ser	Glu	Ile		Gly	Ile	Thr	Ile		Trp	Lys	Phe	Asp				
	865	Gl 11	7~~	λcn	Lou	870	7 cm	Lou	Tuc	Dro	875	Thr	Th.	7~~	Asp	880. Dhe			
	PIO	GIU	A. 9	VOII	885	пр	Mali	Бец	шуъ	890	FILE	1111	1111	Arg	895	FIIC .			
15	Ser	Ile	Arg	Ser		Ala	Asp	Arg	Leu		qaA	Leu	Ser	Tyr	Leu	Ile			
				900			-	_	905	-	•			910					
	Tyr	Val		Pro	Asp	Arg	Pro		Asp	Glu	Val	Phe	Ser	Lys	Tyr	Tyr			
	-1		915		- 1			920		~1	_		925		~ 3	-1.			
20	Thr	930	vaı	Leu	Ala	гуs	935	Val	Asp	GIY	Tyr	940	Lys	Pro	Gln	11e			
20	Lvs		Val	Val	Pro	Glu		Val	Δen	Δla	Ser		Δsn	Ala	Gly	Glv			
	945					950		, uz			955				U -1	960			
	Ser	Ser	Ala	Thr	Tyr	Met	Asp	Gln	Ala	Pro	Ser	Pro	Ala	Val	Cys	Pro	•		
					965					970			_		975				
25	Gln	Ala	Pro	_	Asn	Met	Tyr	Pro		Asn	Pro	Asp	His		Leu	qaA			
	Gln	Acn	Glv	980 Glu	Dhe	Acn	I.em	Δαη	985	Thr	Met	Agn	Val	990 Ala	Arg	His			
	0111	nop	995	Olu	1110	wpp		1000	OIU	1111	Mee	_	1005	niu	9	*****			
	Val	Glu	Glu	Leu	Leu	Arg			Met	Asp	Ser	Leu	Asp	Ser	Arg	Leu			
30		1010					1015					1020		•					
		Pro	Pro	Ala	_		Phe	Thr	Ser		_	Gly	Ser	Leu	Ser				
	025					1030					1035				-	l	•		
			(2)) IN	FORM	ATIO	N FO	R SE	o ID	NO:	56:		•						
35			,-,																
		(:	i) SI	EQUE	ICE (CHAR	ACTE	RIS T :	ICS:										
								se pa	airs										
				TYPI					_										
40				TOP				ingle r	e										
40			(2)	102	J		Inca.											,	
		(:	ii) I	MOLE	CULE	TYP	E: c	DNA											
		(:	ix) 1	FEAT	JRE:	·													
45					/		31	_											
45) LO				ng S	eque	nce									
				OT															
	•		•																
		(:	ki) :	SEQU	ENCE	DES	CRIP	TION	: SE	Q ID	NO:	56:							
50					•														
															CCC			48	
	Met 1	нта	нтα	ATS	AIA 5	ΑΙΑ	АТА	Pro	GIY	Gly 10	GIÀ	СŢΫ	СΙŻ	GIU	Pro 15	Arg			
	_				ر					10								•	
55	GGA	ACT	GCT	GGG	GTC	GTC	CCG	GTG	GTC	CĆC	GGG	GAG	GTG	GAG	GTG	GTG		96	
	Gly	Thr	Ala	Gly	Val	Val	Pro	Val	Val	Pro	Gly	Glu	Val	Glu	Val	Val			
																		•	117

						110		-		
		20			25			30		
5								CTG Leu		144
10								GAC Asp		192
								GAG Glu		240
15								CTG Leu		288
20								GCG Ala 110		336
25								ATG Met		384
30								GAC Asp	•	432
								ATA Ile		480
35								CTT Leu		528
40								CGG Arg 190		576
45								GTG Val		624
50								GGC Gly		672
								GAG Glu		720
55								CAG Gln		768

					245					250					255		
•	CAC	ATT	CTA	GGT	ATC	TTG	GGT	TCC	CCA	TCC	CAG	GAG	GAC	CTT	AAT	TGC	816
_	His	Ile	Leu	_	Ile	Leu	Gly	Ser		Ser	Gln	Glu	qaA		Asn	Cys	
5				260					265					270			
. ,		TTA															864
	Ile	Ile	Asn 275	Met	Lys	Ala	Arg	Asn 280	Tyr	Leu	Gln	Ser	Leu 285	Pro	Ser	Lys	
10																	
		AAG														_	912
	Thr	Lys 290	vaı	MIG	пр	Ала	295	Leu	PHE	PIO	пур	300	Asp	per	пуъ	AIG .	
4.5																	252
15		GAC Asp														_	960
	305	710F				310					315			- <i>y</i> -	5	320	
	מ כי	GTA	CNC	C	ccc	CTTC	COT	C) C	CCT	T N C	CTC	CAA	CAC	ምአ ር	TTA C	CAT	1008
20		Val															1000
					325					330				•	335	•	
	CCG	ACA	СУТ	GAG	CCA	СТС	GCC	GAG	GAG	CCA	ጥጥር	אככ	ጥጥሮ	GAC	ътс	GAG	1056
		Thr															1050
25				340					345					350			
	CTG	GAT	GAC	CTC	CCC	AAG	GAG	CGG	CTG	AAG	GAG	TTG	ATC	TTC	CAG	GAG	1104
	Leu	Asp	_	Leu	Pro	Lys	Glu	_	Leu	Lys	Glu	Leu		Phe	Gln	Glu	
30			355					360		•			365				
	ACA	GCC	CGC	TTC	CAG	CCA	GGG	GCG	CCA	GAG	GGC	CCC	GGG	CGC	GCC	ATG	1152
	Thr	Ala	Arg	Phe	Gln	Pro	-	Ala	Pro	Glu	Gly	Pro 380	Gly	Arg	Ala	Met	٠
		370					375					360					
35		AAA															1200
	Ser 385	Lys	GIY	Glu	Glu	Leu 390	Phe	Thr	GIA	Val	Val 395	Pro	Ile	Leu	Val	G1u 400	
	303					330					,,,						
40		GAT															1248
40	Leu	Asp	GIY	Asp	va1 405	Asn	GIY	GIN	гуѕ	410	ser	vaı	ser	GIA	415	GIÀ	
		GGT															1296
45	GIU	Gly	Asp	420	Inr	Tyr	GIŸ	nys	425	THE	Leu	пÄв	Pne	430	Cys	1111	
•																	
		GGG Gly															1344
•	1111	Gry	435	Deu	PLO	Val	PIO	440	PIU	TIIL	пеп		445	1111	DCu	****	
50				 -	 -												
÷		GGT Gly															1392
	- 7 -	450			- ,5		455	~- y	- y -		voh	460		~ _J 3			
EE	a> c	enterior.	mma	7 7 C	7 CT	~~~	3 mc	000		-	m,	_m_	~~~		202	n cm	1440
55		TTT Phe															1440
•										1	-3-				3		

										120								
	465					470					475					480		
5						GAC Asp											1488	
10			_			CTT Leu											1536	
			_			AAC Asn											1584	
15						TAC Tyr											1632	
20						ATT Ile 550			_								1680	
25						CAA Gln											1728	
30						TAT His										,	1776	
						AGA Arg											1824	
35																GAG T	1873	٠.
40	AA		(2)) IN	FORM	ATIO	N FO	R SE	QI Q	NO:	57:						1875	
45		(:	(A) (B) (C)	LENG TYPI STR	GTH: E: a: ANDE:	CHARA 624 mino DNES: Y: 1:	amin acio S: s:	no a d ingl	cids					٠				
50		(7	v) Fl	RAGM	ENT '	TYPI TYPE DES	: in	tern	al	O TD	NO.	57.						
	Met					Ala							Gly	Glu	Pro	Arg		
55	1				5				_	10					15	Val		4.5
																	. 1	120

WO 98/45704 PCT/DK98/00145

•				20					25					30		
	Lys	Gly	Gln 35	Pro	Phe	Asp	Val	Glý 40	Pro	Arg	Tyr	Thr	Gln 45	Leu	Gln	Tyr
5	Ile	Gly 50	Glu	Gly	Ala	Tyr	Gly 55	Met	Val	Ser	Ser	Ala 60	Tyr	Asp	His	Val
•	Arg 65	Lys	Thr	Arg	Val	Ala 70	Ile	Lys	Lys	Ile	Ser 75	Pro	Phe	Glu	His	Gln 80
•	Thr	Tyr	Сув	Gln	Arg 85	Thr	Leu	Arg	Glu	Ile 90	Gln	Ile	Leu	Leu	Arg 95	Phe
10	Arg	His	Glu	Asn 100	Val	Ile	Gly	Ile	Arg 105	Asp	Ile	Leu	Arg	Ala 110	Pro	Thr
	Leu	Glu	Ala 115	Met	Arg	Asp	Val	Tyr 120	Ile	Val	Gln	Asp	Leu 125	Met	Glu	Thr
15	-	Leu 130	Tyr	Lys	Leu	Leu	Lys 135	Ser	Gln	Gln	Leu	Ser 140	Asn	Asp	His	Ile
	Cys 145	Tyr	Phe	Leu	Tyr	Gln 150	Ile	Leu	Arg	Gly	Leu 155	Lys	Tyr	Ile	His	Ser 160
					His 165	-			-	170					175	
20				180	Leu				185					190		
	_		195		Asp			200					205			
25		210			Ala		215					220				
	225				Ile	230			_	_	235					240
		,			1le 245			•	_	250	_		_		255	
30				260	Ile		_		265					270		
			275		Lys			280	_				285			
35		290			Trp		295				_	300				
	305				Asp	310			٠		315					320
					Ala 325					330					335	
40			_	340	Pro				345					350		
			355		Pro			360					365			
45		370			Gln		375					380				
	385				Glu	390			_		395					400
					Val 405	•				410					415	
50				420	Thr				425					430		
			435		Pro			440					445			
55	Tyr	Gly 450	Val	Gln	Cys	Phe	Ser 455	Arg	Tyr	Pro	Asp	His 460		Lys	Gln	His
	N	D1	m1	T	O	7.7 -	31 - 4-		~ 7			3	~ T	~ ~ ~		m _ ~

	465					470					475					480	•
	Ile	Phe	Tyr	Lys	Asp 485	Asp	Gly	Asn	Tyr	Lys 490	Thr	Arg	Ala	Glu	Val 495	Lys	
5	Phe	Glu	Gly	qeA	Thr	Leu	Val	Asn	Arg 505	Ile	Glu	Leu	Lys	Gly 510	Ile	Asp	
٠.	Phe	Lys	Glu 515	_	Gly	Asn	Ile	Leu 520	Gly	His	Lys	Met	Glu 525	Tyr	Asn	Tyr	•
	Asn	Ser 530	His	Asn	Val	Tyr	Ile 535	Met	Ala	Asp	Lys	Pro 540	Lys	Asn	Gly	Ile	
10	545					550					555	_	_		Val	560	
					565					570					Pro 575		
15				580					585					590	Ser		
	-		595		-		_	600					605		Val		
	Ala	Ala 610	Gly	Ile	Thr	His	Gly 615	Met	Asp	Glu	Leu	Tyr 620	Lys	Pro	Gln	Glu	
20			(2)	INI	FORM	ATIO	v FOI	R SE	Q ID	NO:	58:						
25			(A) (B) (C) (D)	EQUENTYPH TYPH STRA	E: nu ANDEI OLOGI	1819 ucle: ONESS Y: l:	5 bas ic ac S: s: ineas	se pa cid ingle	airs								
30		-	ix) I	MOLE(JRE:												
			(B)	NAI LOC OTI	CATIO	ON:	1:	1811	equei	nce							
35		(2	ki) S	SEQUI	ENCE	DES	CRIP'	rion	: SE	Q ID	ΝΟ:	58:					
40								Gly							CAG Gln 15		48
															GAA Glu		96
45															GTT Val		. 144
50															TGT Cys		192
55															GAG Glu		240

			ATC Ile											288
5			TAT Tyr 100											336
10			ACA Thr		_									384
15			CTG Leu											432
20			CTC Leu											480
25		_	TGT Cys			_								528
			GGG Gly 180											576
30			ATT Ile											624
35			GTG Val											672
40			GGA Gly	Lys		Tyr	Leu	Asp	Gln	Leu	Asn			720
45			TCT Ser											768
			AAC Asn 260											816
50			TTG Leu											864
55			TTG Leu											912

		CTG Leu														_	960
5		ATT															1008
10		AAG Lys															1056
15	Gln	CCA Pro	Gly 355	Tyr	Arg	Ser	Met	Asp 360	Pro	Pro	Val	Ala	Thr 365	Met	Val	Ser	1104
20		GGC Gly 370															1152
25		GGC Gly															1200
		GAT Asp															1248
30		AAG Lys															1296
35		GTG Val															1344
40		TTC Phe 450				•											1392
45		TTC Phe															1440
40		GGC Gly															1488
50		GAG Glu								Lys							1536
55		CAC His							Asp					Gly			1584

		AAC Asn 530															1632
5																	
		GAC															1680
ř .	A1a 545	Asp	His	Tyr	GIn	550	Asn	Thr	Pro	11e	222.	Asp	GIÀ	Pro	vaı	ьец 560	
10		CCC Pro															1728
			-14-2		565	-,-				570					575		
		AAC															1776
15	Pro	Asn	Glu	Lys 580	Arg	Asp	His	Met	Val 585	Leu	Leu	Glu	Phe	Val 590	Thr	Ala	
	GCC	GGG	ATC	ACT	CTC	GGC	ATG	GAC	GAG	CTG	TAC	AA (AATE				1815
20		Gly															
			. (2)	T 111	70DM	. m T ()	. E01	. 05/	. TD	NO.	- 0 -						
			(2)	T1/1	CRM	ATTOL	N FOI	K SE	מד ג	NO:	9:						
25		į)	(A) (B)	LENG	GTH: E: ar	CHARI 604 mino	amin acid	no ad	cids								
						ONESS Y: 1:		-	9								
30			(2)	101													•
						TYPI TYPE	_										
35		()	ci) s	SEQUI	ENCE	DES	CRIP'	rion	: SE	Q ID	NO:	59:					
55	Met 1	Ala	Ala	Ala	Ala 5	Ala	Ala	Gly	Pro	Glu 10	Met	Val	Arg	Gly	Gln 15	Val	,
	Phe	Asp	Val	Gly	Pro	Arg	Tyr	Thr	Asn	Leu	Ser	Tyr	Ile	Gly	Glu	Gly	
40	Ala	Tyr	Gly	20 Met	Val	Cys	Ser	Ala		Asp		Leu	Asn	30 Lys	Val	Arg	
	**- 1	27-	35	7	7	77.	0	40	Db.a	01	774 -	0 3	45	m	<i>(</i> 1	<i>C</i> 15	
		Ala 50					55.					60					
45	65	Thr	rea	Arg	GIU	70	гур	116	теп	Leu	75	PILE	Arg	UIR	GIU	80	
		Ile	Gly	Ile	Asn 85	Asp	Ile	Ile	Arg	Ala 90	Pro	Thr	Ile	Glu	Gln 95	Met	
	Lys	Asp	Val	Tyr 100	Ile	Val	Gln	Asp	Leu 105	Met	Glu	Thr	Asp	Leu 110	-	Lys	
50	Leu	Leu	Lys 115		Gln	His	Leu	Ser 120		Asp	His	Ile	Cys 125		Phe	Leu	
	Tyr	Gln 130	Ile	Leu	Arg	Gly	Leu 135	Lys	Tyr	Ile	His	Ser 140		Asn	Val	Leu	•
		Arg	qaA	Leu	Lys		Ser	Asn	Leu	Leu		Asn	Thr	Thr	Cys	Asp	
55	145	Laze	Tle	Cve	Δen	150 Dhe	Glar	Len	- ומ	D~~	155	פוע	Den	Dro	Aen	160 His	
	המת	пλя	TTE	Cyp	чэħ	T. IIC	GIA	neu	wrq	wr.a	val	WTG	vah	-10	vab	1113	

					165					170					175	
	Asp	His	Thr	Gly	Phe	Leu	Thr	Glu	Tyr	Val	Ala	Thr	Arg	Trp	Tyr	Arg
				180					185					190		
	Ala	Pro	Glu	Ile	Met	Leu	Asn	Ser	Lys	Gly	Tyr	Thr	Lys	Ser	Ile	Asp
5			195					200				•	205		•	
	Ile	Trp	Ser	Val	Gly	Cys	Ile	Leu	Ala	Glu	Met	Leu	Ser	Asn	Arg	Pro
		210			_		215		•			220				
	Ile	Phe	Pro	Gly	Lys	His	Tyr	Leu	Asp	Gln	Leu	Asn	His	Ile	Leu	Gly
	225			•	•	230	•		•		235					240
10		Leu	Glv	Ser	Pro		Gln	Glu	Asp	Leu	Asn	Cvs	Ile	Ile	Asn	Leu
					245					250		1			255	
	Lvs	Ala	Ara	Asn		Leu	Leu	Ser	Leu		His	Lvs	Asn	Lvs	Val	Pro
	-,-			260	- 3 -				265			•		270		
	Trn	Asn	Ara		Phe	Pro	Asn	Ala		Ser	Lvs	Ala	Leu		Leu	Leu
15	110		275			,0		280			-1-		285	<u>F</u>		
10	Acn	Lys		Leu	Thr	Phe	Δsn		His	Lvs	Ara	Tle		Val	Glu	Gln
	AGP	290					295			_, _	5	300				
	Δla	Leu	Δla	His	Pro	Tvr		Glu	Gln	Tvr	Tvr		Pro	Ser	asp	Glu
	305	БСС	1114		110	310	בים	Q14	-	- 7 -	315					320
20		Ile	Δla	Glu	Δla		Phe	Lvs	Phe	Asp		Glu	Len	Asp	Asp	
20	110				325			_,_		330				<u>F</u>	335	
	Pro	Lys	Glu	Lvs		Lvs	Glu	Leu	Tle		Glu	Glu	Thr	Ala		Phe
		-,-		340		-,-			.345					350	_	
	Gln	·Pro	Glv		Ara	Ser	Met			Pro	Val	Ala	Thr	Met	Val	Ser
25			355	- 7 -	5			360					365			
	Lvs	Gly	Glu	Glu	Leu	Phe	Thr	Gly	Val	Val	Pro	Ile	Leu	Val	Glu	Leu
	_,	370					375	•				380				
	Asp	Gly	Asp	Val	Asn	Gly	His	Lys	Phe	Ser	Val	Ser	Gly	Glu	Gly	Glu
	385		-			390		•	•		395		-		_	400
30	Gly	Asp	Ala	Thr	Tyr	Gly	Lys	Leu	Thr	Leu	Lys	Phe	Ile	Cys	Thr	Thr
	-	-			405	-	_			410	-				415	
	Gly	Lys	Leu	Pro	Val	Pro	Trp	Pro	Thr	Leu	Val	Thr	Thr	Leu	Thr	Tyr
	-			420					425					430		
	Gly	Val	Gln	Cys	Phe	Ser	Arg	Tyr	Pro	Asp	His	Met	Lys	Gln	His	Asp
35			435					440			•		445			
	Phe	Phe	Lys	Ser	Ala	Met	Pro	Glu	Gly	Tyr	Val	Gln	Glu	Arg	Thr	Ile
		450					455					460				
	Phe	Phe	Lys	Asp	Asp	Gly	Asn	Tyr	Lys	Thr	Arg	Ala	Glu	Val	Lys	Phe
	465					470					475					480
40	Glu	Gly	Asp	Thr	Leu	Val	Asn	Arg	Ile	Glu	Leu	Lys	Gly	·Ile	qeA	Phe
					485					490	•				495	
	Lys	Glu	Asp	Gly	Asn	Ile	Leu	Gly	His	Lys	Leu	Glu	Tyr	Asn	Tyr	Asn
				500					505					510		
	Ser	His	Asn	Val	Tyr	Ile	Met	Ala	Asp	Lys	Gln	Lys	Asn	Gly	Ile	Lys
45	•		515					520					525			
	Val	Asn	Phe	Lys	Ile	Arg	His	Asn	Ile	Glu	Asp	Gly	Ser	Val	Gln	Leu
		530					535					540				
	Ala	Asp	His	Tyr	Gln	Gln	Asn	Thr	Pro	Ile	Gly	Asp	Gly	Pro	Val	Leu
	545					550					555					560
50	Leu	Pro	Asp	Asn	His	Tyr	Leu	Ser	Thr	Gln	Ser	Ala	Leu	Ser	Lys	Asp
					565					570					575	•
	Pro	Asn	Glu	Lys	Arg	Asp	His	Met	Val	Leu	Leu	Glu	Phe	Val	Thr	Ala
				580					585					590		
	Ala	Gly		Thr	Leu	Gly	Met	_		Leu	Tyr	Lys				
55			595			•		600								

(2) INFORM	NOITAN	FOR	SEQ	ID	NO:60:
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5		(A) (B) (C) (D)	TYPE STRA	ICE C STH: E: nu ANDEL OLOGY	2511 clei NESS	bas c ac : si near	e pa id ngle	irs					
10	-	ix) I	TEAT	TRE:									
15	. (2	(B)	LOC	ME/KE CATIO HER I	N: 1 NFOR	RMATI	508 ON:		NO: 6	50:			
20	 			AAC Asn 5									48
. 25				GGA Gly									96
25				CCT Pro									144
30	 			TAC Tyr									192
35	 			CAG Gln									240
40				GAC Asp 85									288
45				AAA Lys									336
				TTC Phe									384
50				CTC Leu								GCC Ala	432
55	Ala											GAA Glu 160	480

								CAG Gln					528
5								CAG Gln					576
10								CAG Gln					624
15								AAG Lys 220					672
20								CAG Gln					720
25				Val				GCC Ala				AAG Lys	768
20								GGG Gly					816
30								GAG Glu		Glu			864
35								GAA Glu 300					912
40								AAC Asn					960
45								TTG Leu				Ile	1008
45							Val	ACT Thr			Tyr	ATG Met	1056
50						Arg				Pro		TAC Tyr	1104
55		Leu			Tyr				Gly			CCG Pro	1152

5		CGC Arg															1200
		CTG Leu															1248
10		TCC Ser															1296
15		TGC Cys															1344
20		AAC Asn 450															1392
25	Phe 465	GTT Val	Pro	Asp	Pro	Arg 470	Ala	Val	Tyr	Cys	Lys 475	Asp	Val	Leu	Asp	Ile 480	1440
	Glu	CAG Gln	Phe	Ser	Thr 485	Val	Lys	Gly	Val	Asn 490	Leu	Asp	His	Thr	Asp 495	Asp	1488
30	Asp	TTC Phe	Tyr	Ser 500	Lys	Phe	Ser	Thr	Gly 505	Ser	Val	Ser	Ile	Pro 510	Trp	Gln	1536
35	Asn	GAG Glu	Met 515	Ile	Glu	Thr	Glu	Cys 520	Phe	Lys	Glu	Leu	Asn 525	Val	Phe	Gly	1584
40	Pro	AAT Asn 530	Gly	Thr	Leu	Pro	Pro 535	Asp	Leu	Asn	Arg	Asn 540	His	Pro	Pro	Glu	1632
45		CCC Pro										Lys					1680
		AAT Asn									Thr					His	1728
50		AAC Asn			His					Ser					Arg		1776
55				Ala					Lys					Phe		GGG Gly	1824

												•
E								GTA Val 620				1872
5		 						ACC Thr				1920
10	ACC Thr							CCC	_			1968.
15								TGC Cys				2016
20								TCC Ser				2064
25		Val						GAC Asp 700				2112
								ACC Thr				2160
30								GGC Gly				2208
35								GTC Val				2256
40					Val			AAG Lys				2304
45	Ile							TAC Tyr 780				2352
45								AAC Asn				2400
50							Glu	AAG Lys				2448
55			Phe			Gly				Met	GAC Asp	2496

GAG CTG TAC AAG TAA Glu Leu Tyr Lys 835

2511

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(2) INFORMATION FOR SEQ ID NO:61:

- (i) SEQUENCE CHARACTERISTICS:
 - (A) LENGTH: 836 amino acids
 - (B) TYPE: amino acid
 - (C) STRANDEDNESS: single
 - (D) TOPOLOGY: linear
- 15 (ii) MOLECULE TYPE: protein
 - (v) FRAGMENT TYPE: internal

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:61:

20 Met Glu Leu Glu Asn Ile Val Ala Asn Thr Val Leu Leu Lys Ala Arg Glu Gly Gly Gly Lys Arg Lys Gly Lys Ser Lys Lys Trp Lys Glu Ile Leu Lys Phe Pro His Ile Ser Gln Cys Glu Asp Leu Arg Arg Thr 25 40 Ile Asp Arg Asp Tyr Cys Ser Leu Cys Asp Lys Gln Pro Ile Gly Arg 55 Leu Leu Phe Arg Gln Phe Cys Glu Thr Arg Pro Gly Leu Glu Cys Tyr 70 30 Ile Gln Phe Leu Asp Ser Val Ala Glu Tyr Glu Val Thr Pro Asp Glu 85 90 Lys Leu Gly Glu Lys Gly Lys Glu Ile Met Thr Lys Tyr Leu Thr Pro 105 Lys Ser Pro Val Phe Ile Ala Gln Val Gly Gln Asp Leu Val Ser Gln 35 120 Thr Glu Glu Lys Leu Gln Lys Pro Cys Lys Glu Leu Phe Ser Ala 135 140 Cys Ala Gln Ser Val His Glu Tyr Leu Arg Gly Glu Pro Phe His Glu 150 155 40 Tyr Leu Asp Ser Met Phe Phe Asp Arg Phe Leu Gln Trp Lys Trp Leu 165 170 Glu Arg Gln Pro Val Thr Lys Asn Thr Phe Arg Gln Tyr Arg Val Leu Gly Lys Gly Gly Phe Gly Glu Val Cys Ala Cys Gln Val Arg Ala Thr 45 Gly Lys Met Tyr Ala Cys Lys Arg Leu Glu Lys Lys Arg Ile Lys Lys 215 Arg Lys Gly Glu Ser Met Ala Leu Asn Glu Lys Gln Ile Leu Glu Lys 230 235 50 Val Asn Ser Gln Phe Val Val Asn Leu Ala Tyr Ala Tyr Glu Thr Lys 245 250 Asp Ala Leu Cys Leu Val Leu Thr Ile Met Asn Gly Gly Asp Leu Lys 265 Phe His Ile Tyr Asn Met Gly Asn Pro Gly Phe Glu Glu Glu Arg Ala 55

131

Leu Phe Tyr Ala Ala Glu Ile Leu Cys Gly Leu Glu Asp Leu His Arg

		290					295					300				
	Glu 305	Asn	Thr	Val	Tyr	Arg 310	Asp	Leu	Lys	Pro	Glu 315	Asn	Ile	Leu	Leu	Asp 320
5	Asp	Tyr	Gly	His	Ile 325	Arg	Ile	Ser	Asp	Leu 330	Gly	Leu	Ala	Val	Lys 335	Ile
	Pro	Glu	Gly	Asp 340	Leu	Ile	Arg	Gly	Arg 345	Val	Gly	Thr	Val	Gly 350	Tyr	Met
			355		Leu			360					365			
10	_	370			Cys		375					380				
	385				Lys	390					395					400
15					Glu 405					410					415	
				420	Lys				425					430		
	-	-	435		Glu			440	,				445			
20		450		•	Phe		455					460				
	465				Pro	470					475					480
25					Thr 485					490					495	
	_			500	Lys				505					510		
			515		Glu			520					525			
30		530			Leu		535					540				
•	545				Gly Ser	550					555					560
35			•	-	565 His					570					575	
				580	Thr				585		-			590		
40			595		Leu	•		600					605			
40		610			Gly		615					620				
	625					630					635					640
45					Ile 645					650					655	
				660	Thr				665					670		
50			675		Lys Glu			680					685			
50		690			Glu		695					700				
	705		_		Glu	710					715					720
55					725					730)				735	

																		•	
•				740					745					750					
	Asp	Lys	Gln 755	Lys	Asn	Gly	Ile	Lys 760	Val	Asn	Phe	Lys	Ile 765	Arg	His	Asn			
5	Ile	Glu 770	Asp	Gly	Ser	Val	Gln 775	Leu	Ala	Asp	His	Tyr 780	Gln	Gln	Asn	Thr			
	Pro 785	Ile	Gly	Asp	Gly	Pro 790	Val	Leu	Leu	Pro	Asp 795	Asn	His	Tyr	Leu	Ser 800			
	Thr	Gln	Ser	Ala	Leu 805	Ser	Lys	Asp	Pro	Asn 810	Glu	Lys	Arg	Asp	His 815	Met			
10	Val	Leu	Leu	Glu 820	Phe	Val	Thr	Ala	Ala 825	Gly	Ile	Thr	Leu	Gly 830	Met	Asp			
	Glu	Leu	Tyr 835	Lys								•					•	,	
15			(2)	INI	FORM	TION	I FOR	SEÇ) ID	NO : 6	52:								
		· (i		EQUE															
20			(B)	TYPE STRA	: nı	ıcle	ic ac	id							٠				
20				TOP				_	=					•					
				OLEC		TYPI	E: cI	ONA									•		
25				IAN (EY: (Codir	ıg Se	eque	ıce									
		•		LOC															
30		()	ci) S	SEQUI	ENCE	DES	CRIP:	rion	: SE(Q ID	NO : 6	62:		*					
														GAG Glu				48	
35	1		5		5		·			10	-1-				15	•			
			-				-		-					AAA Lys				96	
				20					25					30					
40			Gly					Val					Asp	GCC Ala				144.	
	<i>a</i>	202	35	c.mm	CCN	3.MC	220	40	Cm h	200	CCN	CCN	45	C N C	חממ	CAC	,	192	-
45		Arg												CAG Gln		_		192	
	ልሮሞ	50 CAT	פככ	ממ	ርርር	פרר		AGA	GAG	СТА	ሮ ሞሞ		ΔТС	AAA	TGT	GTT		240	
50	•													Lys		_			
		CAC	AAA	AAT	ATA		GGC	CTT	TTG	AAT		TTC	ACA	CCA	CAG	AAA		288	
														Pro	_				
55	TCC	CTA	GAA	GAA	TTT	CAA	GAT	GTT	TAC	ATA	GTC	ATG	GAG	CTC	ATG	GAT		336	
																٠			133

										10-1							
	Ser	Leu	Glu	Glu 100	Phe	Gln	Asp	Val	Tyr 105	Ile	Val	Met	Glu	Leu 110	Met	Asp	
	GCA	AAT	بلبلب	TGC	CAA	GTG	αππ	CAG	ATG	GAG	ΔТЭ	CAT	СУТ	AAD	AGA	ΔTG	384
5		Asn															204
3	Ala	M211	115	Cys	GIII	vai	116		MEC	GIU	пеп	Asp		GIU	Arg	MEC	
			115					120					125		•		•
	maa	m		ama	m » m	a	3 mc	ama	mam		3 ma		~~~	amm	~~	mam	420
		TAC															432
	ser	Tyr	Leu	Leu	Tyr			Leu	Cys	GIA	He	_	His	Leu	His	Ser	
10		130		•			135					140					
									•								
	GCT	GGA	ATT	ATT	CAT	CGG	GAC	TTA	AAG	CCC	AGT	AAT	ATA	GTA	GTA	AAA	480
	Ala	Gly	Ile	Ile	His	Arg	Asp	Leu	Lys	Pro	Ser	Asn	Ile	Val	Val	Lys	-
	145					150					155					160	
15																	
	TCT	GAT	TGC	ACT	TTG	AAG	ATT	CTT	GAC	TTC	GGT	CTG	GCC	AGG	ACT	GCA	528
	Ser	Asp	Cys	Thr	Leu	Lys	Ile	Leu	Asp	Phe	Gly	Leu	Ala	Arg	Thr	Ala	
					165	_				170	_			_	175	•	
													•				
20	GGA	ACG	AGT	TTT	ATG	ATG	ACG	CCT	TAT	GTA	GTG	ACT	CGC	TAC	TAC	AGA	576
		Thr															
				180					185				3	190	-3-	· J	
	GCA	CCC	GAG	GTC	ΔΤС	СТТ	GGC	ATG	GGC	TAC	DAG	AAD	AAC	GTG	GAT	TTA	624
25		Pro															5. 1
20	ALG	110	195	vul		LCu	Cly	200	Cly	- y -	Lyb		205	Val	пор	Dea	
			173					200					203				
	TCC	TCT	СТС	ccc	TOO	א שיש	አጥር	CGA	CAA	איניכי	CTT	TCC	CAC	מממ	አጥሮ	CTC	672
		Ser															072
30	пр		val	GIY	Сув	TIE		GIY	GIU	MEL	vai	_	UTS	nys	116	Deu	
30		210					215					220					
	mmm	a aa	CC3	3.00	a. a	mam	* 100	. Cl 3 m	a. a	maa	3 3 77		OMM.	a mm	~~~	C2.C	720
		CCA															720
		Pro	GIY	Arg	Asp	_	тте	Asp	GIN	Trp		гуя	vaı	ттё	GIU		
0.5	225					230					235					240	•
35																	
		GGA															768
	Leu	Gly	Thr	Pro	Cys	Pro	Glu	Phe	Met	Lys	Lys	Leu	Gln	Pro		Val	
					245					250					255		
40		ACT															816
	Arg	Thr	Tyr	Val	Glu	Asn	Arg	Pro	Lys	Tyr	Ala	Gly	Tyr	Ser	Phe	Glu	
				260					265					270			
								TTC	CCA	CCT	GAC	TCA	GAA	CAC	מממ	מממ	864
	AAA	CTC	TTC	CCT	GAT	GTC	CTT	TIC	CCA		Cric		0.11	Cric	71110		004
45		CTC Leu						_									004
45								_									
45			Phe					Phe					Glu				
45	Ĺys		Phe 275	Pro	Asp	Val	Leu	Phe 280	Pro	Ala	Asp	Ser	Glu 285	His	Asn	Lys	
45	Lys	Leu	Phe 275 GCC	Pro AGT	Asp	Val GCA	Leu AGG	Phe 280 GAT	Pro	Ala	Asp	Ser	Glu 285 ATG	His CTG	Asn GTA	Lys	
	Lys	Leu AAA	Phe 275 GCC	Pro AGT	Asp	Val GCA	Leu AGG	Phe 280 GAT	Pro	Ala	Asp	Ser	Glu 285 ATG	His CTG	Asn GTA	Lys	
45 50	Lys	Leu AAA Lys	Phe 275 GCC	Pro AGT	Asp	Val GCA	Leu AGG Arg	Phe 280 GAT	Pro	Ala	Asp	Ser AAA Lys	Glu 285 ATG	His CTG	Asn GTA	Lys	
	Lys CTT Leu	Leu AAA Lys	Phe 275 GCC Ala	Pro AGT Ser	Asp CAG Gln	Val GCA Ala	AGG Arg 295	Phe 280 GAT Asp	Pro TTG Leu	Ala TTA Leu	Asp TCC Ser	AAA Lys 300	Glu 285 ATG Met	His CTG Leu	Asn GTA Val	Lys ATA Ile	
	Lys CTT Leu GAT	AAA Lys 290 GCA	Phe 275 GCC Ala TCT	Pro AGT Ser	CAG Gln AGG	Val GCA Ala ATC	AGG Arg 295	Phe 280 GAT Asp	Pro TTG Leu GAT	Ala TTA Leu GAA	TCC Ser	AAA Lys 300	Glu 285 ATG Met	CTG Leu	Asn GTA Val	Lys ATA Ile	912
	CTT Leu GAT Asp	AAA Lys 290	Phe 275 GCC Ala TCT	Pro AGT Ser	CAG Gln AGG	GCA Ala ATC	AGG Arg 295	Phe 280 GAT Asp	Pro TTG Leu GAT	Ala TTA Leu GAA	TCC Ser GCT Ala	AAA Lys 300	Glu 285 ATG Met	CTG Leu	Asn GTA Val	ATA Ile TAC	912
50	Lys CTT Leu GAT	AAA Lys 290 GCA	Phe 275 GCC Ala TCT	Pro AGT Ser	CAG Gln AGG	Val GCA Ala ATC	AGG Arg 295	Phe 280 GAT Asp	Pro TTG Leu GAT	Ala TTA Leu GAA	TCC Ser	AAA Lys 300	Glu 285 ATG Met	CTG Leu	Asn GTA Val	Lys ATA Ile	912
	CTT Leu GAT Asp 305	AAA Lys 290 GCA	Phe 275 GCC Ala TCT Ser	AGT Ser AAA Lys	CAG Gln AGG Arg	GCA Ala ATC Ile 310	AGG Arg 295 TCT Ser	Phe 280 GAT Asp GTA Val	Pro TTG Leu GAT Asp	Ala TTA Leu GAA Glu	TCC Ser GCT Ala 315	AAA Lys 300 CTC Leu	Glu 285 ATG Met CAA Gln	CTG Leu CAC	Asn GTA Val CCG Pro	ATA Ile TAC Tyr 320	912

																	•	
	Ile	Asn	Val	Trp	Tyr 325	Asp	Pro	Ser	Glu	Ala 330	Glu	Ala	Pro	Pro	Pro 335	Lys		
5				AAG Lys 340													1056	•
10				ATA Ile													1104	
45				ATA Ile												CAG Gln	1152	
15				CCG Pro													1200	
20				GTG Val													1248	
25				AGC Ser 420													1296	
30				CTG Leu													1344	
35				CTC Leu													1392	
30				GAC Asp													1440	
40				TAC Tyr													1488.	
45				ACC Thr 500													1536	
50				GAG Glu										Gly			1584	
			His	AAG Lys				Asn					Asn			ATC Ile	1632	
55	ATG	GCC	GAC	AAG	CAG	AAG	AAC	GGC	ATC	AAG	GTG	AAC	TTC	AAG	ATC	CGC	1680	135

									,	136							
	Met 545	Ala	Asp	Lys	Gln	Lys 550	Asn	Gly	Ile	Lys	Val 555	Asn	Phe	Lys	Ile	Arg 560	•
5														TAC Tyr			1728
10														AAC Asn 590			1776
														AAG Lys			1824
15														ACT Thr			1872
20				CTG Leu	•		TAA				٠						1893
25								R SE(NO:	53:						
30			(A) (B) (C) (D)	LENG TYPI STRA	ETH: E: ar ANDEI OLOGY	630 mino ONESS	amin acio 3: s: inean	ingle c	eids								
35		. (7	7) FI	RAGMI	ENT :	TYPE	int	rote: terna TION	al	Q ID	NO:	63:					
	Met 1	Ser	Arg	Ser	Lys 5	Arg	qaA	Asn	Asn	Phe 10	туг	Ser	Val	Glu	Ile 15	Gly	
40	_			20					25					Lys			
	_		35					40					45			Leu	
45		50					55					60				Val	
	65 Asn	His	Lys	Asn	Ile	70 Ile	Gly	Leu	Leu		75 Val	Phe	Thr	Pro		80 Lys	
50	Ser	Leu	Glu		85 Phe	Gln	Asp	Val	Tyr 105		Val	Met	Glu	Leu 110		Asp	
	Ala	Asn	Leu 115	100 Cys	Gln	Val	Ile	Gln 120			Leu	Asp	His 125	Glu		Met	
55	Ser	Tyr 130		Leu	Tyr	Gln	Met 135		Cys	Gly	Ile	Lys 140		Leu	His	Ser	
	Ala	Gly	Ile	Ile	His	Arg	Asp	Leu	Lys	Pro	Ser	Asn	Ile	Val	Val	Lys	

	145					150					155					160
	Ser	Asp	Cys	Thr	Leu 165	Lys	Ile	Leu	Asp	Phe 170	Gly	Leu	Ala	Arg	Thr 175	Ala
5	Gly	Thr	Ser	Phe 180	Met	Met	Thr	Pro	Tyr 185	Val	Val	Thr	Arg	Tyr 190	Tyr	Arg
	Ala	Pro	Glu 195	Val	Ile	Leu	Gly	Met 200	Gly	Tyr	Lys	Glu	Asn 205	Val	Asp	Leu
	Trp	Ser 210	Val	Gly	Сув	Ile	Met 215	Gly	Glu	Met	Val	Cys. 220	His	Lys	Ile	Leu
10	Phe 225	Pro	Gly	Arg	Asp	Tyr 230	Ile	Asp	Gln	Trp	Asn 235	Lys	Val	Ile	Glu	Gln 240
	Leu	Gly	Thr	Pro	Cys 245	Pro	Glu	Phe	Met	Lys 250	Lys	Leu	Gln	Pro	Thr 255	Val
15	Arg	Thr	Tyr	Val 260	Glu	Asn	Arg	Pro	Lys 265	Tyr	Ala	Gly	Tyr	Ser 270	Phe	Glu
	-		275					280			_		285	His		
		290					295	*				300		Leu		
20	305					310			_		315			His		320
					325					330				Pro	335	
25	Ile			340					345				•	350		
	-		355		_	-		360		_			365	Arg		
20		370				_	375					380		Val		
30	385					390					395			Glu Val		400
					405					410	_	_			415	Gly
35		_		420			_		425					430 Pro		
	-		435					440					445	Cys		
40		450					455					460				Met
40	465	_		_		470	_			_	475		_	Asp		480
			_	_	485	,				490					495	Val
45			_	500					505					510		Ile
		_	515			_		520	_				525			Ile
50		530					535		_			540				Arg
	545				Asp	550				Leu	555 Ala				Gln	560 Gln
EE	Asn	Thr	Pro		565 Gly	Asp	Gly	Pro		570 Leu		Pro	Asp	Asn	575 His	
55	Leu	Ser	Thr	580 Gln	Ser	Ala	Leu	Ser	585 Lys	Asp	Pro	Asn	Glu	590 Lys	Arg	Asp

•	uic.		595 Val	I.eu	I.en	Glu		600 Val	Thr	Ala	Ala	Glv	605 Ile	Thr	Leu	Glv		
		610					615			•		620				·		
5	Met 625	Asp	Glu	Leu		Lys 630												
			(2)	INF	ORMA	TION	FOR	SEQ	ID	NO : 6	4:							
		(i) SE	_														
10			(B) (C)	LENG TYPE STRA TOPO	: nu	clei NESS	c ac	id ngle										
15			li) M lx) F			TYPE	: cD	ANG										
20		•	(B)	NAM LOC	ATIC	N: 1	1	818	equer	ıce						•		
		()	(i) S	EQUE	ENCE	DESC	RIPI	ION:	: SEÇ	Q ID	NO : 6	54:						
	ATG	тст	CAG	GAG	AGG	CCC	ACG	TTC	TAC	CGG	CAG	GAG	CTG	AAC	AAG	ACA	48	
25													Leu					
													CCA				96	
30	Ile	Trp	Glu	20	Pro	GIU	Arg	Tyr	25	ASN	ьеи	Ser	Pro	30	GIY	Ser		
													AAA				144	
	Gly	Ala	Tyr 35	GIÀ	Ser	Val	Cys	40	Ala	Pne	Asp	THE	Lys 45	THE	GIY	Deu		
35													TCC				192	
	Arg	Val 50	Ala	Val	Lys	Lys	Leu 55	Ser	Arg	Pro	Phe	Gln 60	Ser	Ile	Ile	His		
40	GCG	AAA	AGA	ACĊ	TAC	AGA	GAA	CTG	CGG	TTA	CTT	AAA	CAT	ATG	AAA	CAT	240	
	Ala 65	Lys	Arg	Thr	Tyr	Arg 70	Glu	Leu	Arg	Leu	Leu 75	Lys	His	Met	Lys	His 80		
	GAA	AAT	GTG	ATT	GGT	CTG	TTG	GAC	GTT	TTT	ACA	CCT	GCA	AGG	TCT	CTG	288	
45													Ala			Leu		
	GNG	GDA	ጥጥር	ልልጥ		GTG	ጥልጥ	СТС	GTG		САТ	СТС	ATG	GGG	GCA	GAT	336	
50				Asn					Val	Thr					Ala	Asp		
50				100					105			~				י מאמ	204	
													Asp	His		CAG Gln	384	
55			115					120					125					
	TTC	CTT	ATC	TAC	CAA	ATT	CTC	CGA	GGI	CTA	AAG	TAT	ATA	. CAT	TCA	A GCT	432	138

	Phe	Leu 130	Ile	Tyr	Gln	Ile	Leu 135	Arg	Gly	Leu	Lys	Tyr 140	Ile	His	Ser	Ala		
5														GTG Val			480	
10														CAC His			528.	
														GCT Ala 190			576	
15														ATT Ile			624	
20														TTG Leu			672	
25														CTC Leu			720	
30	ACC Thr	CCA Pro	GGG Gly	GCT Ala	GAG Glu 245	CTT Leu	TTG Leu	AAG Lys	AAA Lys	ATC Ile 250	TCC	TCA Ser	GAG Glu	TCT	GCA Ala 255	AGA Arg	768	
													Asn	TTT Phe 270			816	
35				Gly					Ala					GAG Glu			864	
40	CTT Leu	GTA Val 290	Leu	GAC Asp	TCA Ser	GAT Asp	AAG Lys 295	Arg	ATT	ACA Thr	GCG Ala	GCC Ala 300	Gln	GCC Ala	CTT	GCA Ala	912	
45	CAT His 305	Ala	TAC	TTT Phe	GCT	CAG Gln 310	Tyr	CAC His	GAT Asp	CCT Pro	GAT Asp 315	Asp	GĀA Glu	CCA Pro	GTG Val	GCC Ala 320	960	
50						Ser					Asp					GAG Glu	1008	
					Thr					Ile					Pro	A CCC D Pro	1056	
55	CTI	GAC	CA	A GAA	GAC	TA S	GAC	TC(C GAG	G GAT	CCI	A CC	G GTO	C GCC	C ACC	C ATG	1104	139

										170								
	Leu	Asp	Gln 355	Glu	Glu	Met	Glu	Ser 360		Asp	Pro.	Pro	Val 365	Ala	Thr	Met		
5				GGC Gly													1152	
10				GGC Gly													1200	
15				GAT Asp											_		1248	
15				AAG Lys 420													1296	
20				GTG Val													1344	
25 [.]				TTC Phe													1392	
30				TTC Phe													1440	
35				GGC Gly													1488	
				GAG Glu 500													1536	
40	TAC Tyr			CAC His													1584	
45				AAC Asn													1632	
50		Leu		GAC Asp			Gln										1680	
											Thr					AGC Ser	1728	
55	AAA	GAC	CCC	AAC	GAG	AAG	CGC	GAT	CAC	ATG	GTC	CTG	CTG	GAG	TTC	GTG	1776	140

Lys Asp Pro Asn Glu Lys Arg Asp His Met Val Leu Leu Glu Phe Val 585 ACC GCC GCC GGG ATC ACT CTC GGC ATG GAC GAG CTG TAC AAG TAA 1821 Thr Ala Ala Gly Ile Thr Leu Gly Met Asp Glu Leu Tyr Lys 5 (2) INFORMATION FOR SEQ ID NO:65: 10 (i) SEQUENCE CHARACTERISTICS: (A) LENGTH: 606 amino acids (B) TYPE: amino acid (C) STRANDEDNESS: single 15 (D) TOPOLOGY: linear (ii) MOLECULE TYPE: protein (v) FRAGMENT TYPE: internal (xi) SEQUENCE DESCRIPTION: SEQ ID NO:65: 20 Met Ser Gln Glu Arg Pro Thr Phe Tyr Arg Gln Glu Leu Asn Lys Thr Ile Trp Glu Val Pro Glu Arg Tyr Gln Asn Leu Ser Pro Val Gly Ser 25 25 Gly Ala Tyr Gly Ser Val Cys Ala Ala Phe Asp Thr Lys Thr Gly Leu 40 Arg Val Ala Val Lys Lys Leu Ser Arg Pro Phe Gln Ser Ile Ile His Ala Lys Arg Thr Tyr Arg Glu Leu Arg Leu Leu Lys His Met Lys His 30 70 75 Glu Asn Val Ile Gly Leu Leu Asp Val Phe Thr Pro Ala Arg Ser Leu 90 Glu Glu Phe Asn Asp Val Tyr Leu Val Thr His Leu Met Gly Ala Asp 35 105 Leu Asn Asn Ile Val Lys Cys Gln Lys Leu Thr Asp Asp His Val Gln 120 125 Phe Leu Ile Tyr Gln Ile Leu Arg Gly Leu Lys Tyr Ile His Ser Ala 135 40 Asp Ile Ile His Arg Asp Leu Lys Pro Ser Asn Leu Ala Val Asn Glu 150 155 Asp Cys Glu Leu Lys Ile Leu Asp Phe Gly Leu Ala Arg His Thr Asp 170 Asp Glu Met Thr Gly Tyr Val Ala Thr Arg Trp Tyr Arg Ala Pro Glu 45 Ile Met Leu Asn Trp Met His Tyr Asn Gln Thr Val Asp Ile Trp Ser 200 Val Gly Cys Ile Met Ala Glu Leu Leu Thr Gly Arg Thr Leu Phe Pro 220 215 50 Gly Thr Asp His Ile Asp Gln Leu Lys Leu Ile Leu Arg Leu Val Gly 235 230 Thr Pro Gly Ala Glu Leu Leu Lys Lys Ile Ser Ser Glu Ser Ala Arg 250 Asn Tyr Ile Gln Ser Leu Thr Gln Met Pro Lys Met Asn Phe Ala Asn 55 265 Val Phe Ile Gly Ala Asn Pro Leu Ala Val Asp Leu Leu Glu Lys Met

			275					280					285			
	Leu	Val 290	Leu	Asp	Ser	Asp	Lys 295	Arg	Ile	Thr	Ala	Ala 300	Gln	Ala	Leu	Ala
5	His 305	Ala	Tyr	Phe	Ala	Gln 310	Tyr	His	Asp	Pro	Asp 315	Asp	Glu	Pro		Ala 320
	Asp	Pro	Tyr	Asp	Gln 325	Ser	Phe	Glu	Ser	Arg 330	Asp	Leu	Leu	Ile	Asp 335	Glu
	Trp	Lys	Ser	Leu 340	Thr	Tyr	Asp	Glu	Val 345	Ile	Ser	Phe	Val	Pro 350	Pro	Pro
10		Asp	355					360					365			
		Ser 370					375					380				
15	385	Leu				390					395					400
	_	Glu			405				•	410					415	
•		Thr		420				•	425					430		
20		Tyr	435		•			440					445			
•		Asp 450					455					460				
25	465	Ile				470					475					480
	_	Phe			485					490					495	
	_	Phe		500					505					510		
30	_	Asn	515					520			-		525			
		530					535					540				Val
35	545			•		550					555					Pro 560
		Leu			565					570					575	
40	_			580					585					590		Val
40	Thr	Ala	595		116	Thr	Leu	600		Asp	Glu	. Deu	605			
			(2) IN	FORM	ATIO	N FO	R SE	Q ID	NO:	66:					
45		(EQUE LEN												•
			(B)	TYP	E: n	ucle	ic a	cid								
50				TOP				_								
				MOLE FEAT			E: c	AND:								
EE) NA						ence						
55				O) OI												

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:66:

		•	-															
5				GAG Glu													4	8
10				GAA Glu 20													•	96
15				TCC Ser												GCC Ala	14	14
				GAA Glu													1:	92
20				GAC Asp													2	40
25				CCT Pro													2	88
30	GTT Val	GCA Ala	CCA Pro	GGT Gly 100	TCT Ser	TCG Ser	AAA Lys	ACT Thr	GAA Glu 105	GCA Ala	GAT Asp	GTT Val	GAA Glu	CAA Gln 110	CAA Gln	GCT Ala		36
35																GCC Ala	3	84
			Leu	CTT													4	32
40	GAA Glu 145	Cys	TCA Ser	ACT Thr	CTA Leu	TAC Tyr 150	Arg	ACA Thr	CAG Gln	AGC Ser	TCC Ser 155	Ser	AAC Asn	CTG Leu	GCA Ala	GAA Glu 160	4	80
45	Leu	Arg	Gln	Leu	Leu 165	Asp	Сув	qaA	Thr	Pro 170	Ser	Val	Asp	Leu	Glu 175			528
50	ATC 11e	GAT Asp	GTG Val	CAC His	Val	TTG Leu	GCT Ala	GAC Asp	GCT Ala 185	Phe	AAA Lys	Arg	TAT Tyr	CTC Leu 190	Leu	GAC Asp	. (576
55	TTA Lev	CCA Pro	AAT Asn 195	Pro	GTC Val	: ATT	CCA	GCA Ala 200	Ala	GTI Val	TAC Tyr	AGT Ser	GAA Glu 205	Met	ATI Ile	TCT Ser		624
-	TTA	A GCT	CCP	A GAA	GTA	CAA	AGC	TCC	GAA	A GAF	A TAT	TATI	CAG	CTP	YTTC	AAG		672

	Leu	Ala 210	Pro	Glu	Val	Gln	Ser 215	Ser	Glu	Glu	Tyr	Ile 220	Gln	Leu	Leu	Lys	
5												TAT Tyr					720
10												CAA Gln					768
,												TTC Phe					816
15												GAA Glu					864
20												GAA Glu 300					912
25												ACT Thr					960
30												GAA Glu					1008
25			Ser									CGA Arg					1056
35												ATG Met					1104
40												TTA Leu 380					1152
45		Arg										TTA Leu					1200
50						Asn					Glu	TCT Ser				Tyr	1248
					Asp					Tyr					Tyr	CAA Gln	1296
55	CAG	GAT	CAA	GTT	GTC	AAA	. GAA	GAT	TAA '	TTA	'GAA	GCI	GTA	GGG	AAA	AAA	1344

	Gln	Asp	Gln 435	Val	Val	Lys	Glu	Asp 440	Asn	Ile	Glu	Ala	Val 445	Gly	Lys	Lys	
5									CAA Gln								1392
٠,		TTA					ACC		ACA			GAA					1440
10	Arg 465	Leu	Tyr	GIu	GIU	17r 470	Thr	Arg	Thr	ser	475	GIU	Пе	GIN	мес	180	
									GAA Glu								1488
15									AGC Ser								1536
	ē			500				. •	505					510			1504
20									ATA Ile								1584
25									GAA Glu								1632
30									GCA Ala								1680
									GAC Asp								1728
35									ACT Thr 585								1776
40									GAA Glu								1824
45			Glu						CCC Pro								1872
50		Val					Arg		AAA Lys			Asn				GGG Gly 640	1920
						Phe			CGG Arg		Ser						1968
55	TAT	GCC	TGC	TCT	GTA	GTG	GTG	GAC	: GGC	GAA	GTA	AAG	CAT	TGI	GTC	ATA :	2016

										140								
	Tyr	Ala	Cys	Ser 660	Val	Val	Val	Asp	Gly 665	Glu	Val	Lys	His	Cys 670	Val ·	Ile	·	
5	AAC Asn																2064	
10														TCC Ser			2112	
15														GTA Val			2160	
														AGC Ser			2208	
20														CTG Leu 750			2256	
25														GAG Glu			2304	
30														ACC Thr			2352	
25														TAC			2400	
35														GAC Asp			2448	
40										Gln						TTC	2496	
45				Gly					Arg					Phe		GGC	2544	
50			Leu					Glu					Asp			GAG Glu	2592	
		Gly					His					Asr				CAC His 880	2640	
55	AAC	GTC	TAT	' ATC	: ATG	GCC	: GAC	AAG	CAC	DAA E	; AAC	: GGC	OTA S	C AAG	GT(AAC	2688	146

										147		•					
	Asn	Val	Tyr .	Ile	Met 885	Ala	Asp	Lys	Gln	Lys 890	Asn.	Gly	Ile	Lys	Val 895	Asn	
5		AAG Lys															2736
10		TAC Tyr															2784
		AAC Asn 930															2832
.15		AAG Lys															2880
20		ACT Thr									TAA						2913
25			(2)	IN	FORM	ATIO	N FO	R.SE	Q ID	NO:	67 [°] :						
30		·	(A) (B) (C) (D)	LENG TYP: STR.	GTH: E: at ANDE OLOG	970 mino DNES Y: 1	ami aci S: s inea	ingl	cids e								
35		•						tern		Q ID	NO:	67:					
40	1				5					10					15	Lys Val	
			35	Ser				40	Gly				45			Ala	
45	_	50					55				Glu	60				Gly Lys	
	65 Lys	Ile	Ser	Pro	Pro	70 Thi	Pro	Lys	Pro	Arg	75 Pro) Pro	Arç	pro) Let	80 1 Pro	
50				100)				105	5				110	כ	n Ala	
			115					120)				125	5		y Leu	
55		130					135	5				140)			a Glu	

	145					150					155					160
	Leu	Arg	Gln	Leu	Leu	Asp	Cys	Asp	Thr	Pro	Ser	Val	qaA	Leu	Glu	Met
					165					170					175	
	Ile	Asp	Val	His	Val	Leu	Ala	Asp	Ala	Phe	Lys	Arg	Tyr	Leu	Leu	Asp
5 .		_		180					185					190		
•	Leu	Pro	Asn	Pro	Val	Ile	Pro	Ala	Ala	Val	Tyr	Ser	Glu	Met	Ile	Ser
			195					200			-		205		•	
	Len	Δla		Glu	Val	Gln	Ser	Ser	Glu	Glu	Tyr	Ile	Gln	Leu	Leu	Lys
	Dea	210					215				•	220				
10	LVC		Tle	Ara.	Ser	Pro		Ile	Pro	His	Gln	Tyr	Trp	Leu	Thr	Leu
10	225	пси				230					235		•			240
		ጥኒም	T.e.11	ī.en	Lvs		Phe	Phe	Lvs	Leu		•	Thr	Ser	Ser	Lys
	GIII	TYL	ДСи	200	245					250					255	-
	7	T 011	Lou	λαη		Δra	Va l	ĩ.eu	Ser		Tle	Phe	Ser	Pro	Met	Leu
45	ASII	Leu	ьeu	260	Ala	AIG	VAI	Deu	265	GIU	110			270		
15	nh -	2 ~~	Dho			תות	Cor	Cor		Acn	Thr	Glu	Δsn	Leu	Tle	Lvs
	Pne	Arg		ser	Ald	AId	Ser	280	АБР	Abii	1111	GIU	285	u		_,_
			275	- 1 -	T	~ 1_	0		σ2	П~~	A o n	Glu		Gln	Dro	Δla
	Val		GIU	TTE	тел	тте		THE	GTu	пр	ASII	300	мц	Gln	110	niu
		290	_	_	_	_	295	_		D	m\		17-1	ת ו ת	7.55	Acn
20		Ala	Leu	Pro	Pro		Pro	Pro	гÀг	Pro		THE	vai	Ala	ASII	320
	305					310	_	_			315	a 3	m	The east	Massa	
	Gly	Met	Asn	Asn		Met	Ser	Leu	GIn		Ala	GIU	тр	Tyr		GIY
					325		_			330	_	_	•	m\	335	7
	Asp	Ile	Ser	-	Glu	Glu	Val	Asn		Lys	Leu	Arg	Asp	Thr	Ala	Asp
25				340					345				•	350		
	Gly	Thr		Leu	Val	Arg	Asp		Ser	Thr	Lys	Met		Gly	Asp	ıyr
			355					360					365			
	Thr	Leu	Thr	Leu	Arg	Lys	Gly	Gly	Asn	Asn	Lys		Ile	Lys	Ile	Phe
		370					375					380				_
30	His	Arg	Asp	Gly	Lys	Tyr	Gly	Phe	Ser	Asp	Pro	Leu	Thr	Phe	Ser	
	385					390					395					400
	Val	Val	Glu	Leu	Ile	Asn	His	Tyr	Arg	Asn	Glu	Ser	Leu	Ala	Gln	Tyr
					405					410					415	
	Asn	Pro	Lys	Leu	Asp	Val	Lys	Leu	Leu	Tyr	Pro	Val	Ser	Lys	Tyr	Gln
35				420					425					430		
	Gln	Asp	Gln	Val	Val	Lys	Glu	Asp	Asn	Ile	Glu	Ala	Val	Gly	Lys	Lys
		_	435					440					445			·
	Leu	His	Glu	Tyr	Asn	Thr	Gln	Phe	Gln	Glu	Lys	Ser	Arg	Glu	Tyr	Asp
		450		-			455					460				
40.	Arq	Leu	Tyr	Glu	Glu	Tyr	Thr	Arg	Thr	Ser	Gln	Glu	Ile	Gln	Met	Lys
	465		•			470		_			475					480
	Ara	Thr	Ala	Ile	Glu	Ala	Phe	Asn	Glu	Thr	Ile	Lys	Ile	Phe	Glu	Glu
	و د				485					490		_			495	
	Gln	Cvs	Gln	Thr			Arq	Tyr	Ser	Lys	Glu	Tyr	Ile	Glu	Lys	Phe
45		- 1-		500				•	505			_		510		
70	Lve	Δra	Glu			Glu	Lvs	Glu			Arc	Ile	Met	His	Asn	Tyr
	цуо	5	515					520			_		525			
	7 cm	Tage			Ser	Aro	Tle			Ile	Ile	Asp	Ser	Arq	Arq	Arg
	АБР	530		. Lys	001	7-9	535		014			540				_
50	T 011			λον	Lan	Lare			בומי	Δla	Gl:			. Glu	Ile	Asp
50			GIU	. wah	. Heu	. Буз 550		, (11)			555		:	,		560
	545	7	MAL	7.~-	6~~			, n~-	Acr	1.0			ים. ז	1 Arc	Lve	Thr
	пÀв	Arg	rie L	. ADI	565		. Lys	, ,,,,	, wah	570				3	575	
	70	. > ~		Tr~			- m	. T.e.	ነ ሞኮ~			יום:	, Val	Arc		Lys
e e	Arg	Asp	GID			Het	. 11E	, הבר	585		. Jys	, 51	743	590		
55		. •	n	580		T					י לידו	- G1:	ı Nev			Ser
	ГÀ	Leu	ASI	ı GIV	LIT	- тел	r GT	/ ASI	1 GTE	ı ASI	1 1111	. 616	. Asi	ווט י	yı	Ser

			595					600					605			
	7	11- 7		7.00	7 ~~	C1	7.00		Dro	ui.	uic) cn		Lys	ጥኮኍ	Trn
	Leu		GIU	Asp	Asp	GIU	615	пеп	PIO	ura	HID	620	Giu	пуъ	1111	TTP
	7 ~~	610	Clv	802	Ser	λen		Λen	Tage	בומ	Glu		I.em	Leu	Ara	Glv
5	625	Val	Gry	Ser	361	630	Arg	Hall	шуз	AIG	635	AOII	Deu	DCu	AL 9	640
3		720) en	Glv	ጥኮኍ		T. A 11	บลา	Δνα	Glu		Ser	Lvs	Gln	Glv	
	пув	Arg	тэр	GIY	645	FIIC	псп	Val	AL 9	650	-	JC1	Dy 5	Q.1.1.	655	Cys
	Tur	פומ	Cvs	Ser		Val	Val	Δsn	Glv		Val:	Lvs.	His	Cys		Ile
	ıyı	ATO	Cys	660	V LL L	V U, I	Vai	пор	665	014		_,_,		670		
10	Agn	LVS	Thr		Thr	Glv	Tvr	Glv		Ala	Glu	Pro	Tvr	Asn	Leu	Tvr
10	ADII	ביים	675				-1-	680					685			-,2
	Ser	Ser		Lvs	Glu	Leu	Val		His	Tvr	Gln	His		Ser	Leu	Val
	501	690		-1-			695			- 2 -		700				
	Gln		Asn	Asp	Ser	Leu		Val	Thr	Leu	Ala	Tyr	Pro	Val	Tyr	Ala
15	705					710					715	•			•	720
			Arq	Arq	Gln	Asp	Pro	Pro	Val	Ala	Thr	Met	Val	Ser	Lys	Gly
			_	_	725	•				730					735	_
	Glu	Glu	Leu	Phe	Thr	Gly	Val	Val	Pro	Ile	Leu	Val	Glu	Leu	Asp	Gly
				740					745					750		
20	Asp	Val	Asn	Gly	His	Lys	Phe	Ser	Val	Ser	Gly	Glu	Gly	Glu	Gly	Asp
	-		755					760					765			
	Ala	Thr	Tyr	Gly	Lys	Leu	Thr	Leu	Lys	Phe	Ile	Cys	Thr	Thr	Gly	Lys
		770					775					780				
	Leu	Pro	Val	Pro	Trp	Pro	Thr	Leu	Val	Thr	Thr	Leu	Thr	Tyr	Gly	Val
25	785					790					795					800
	Gln	Сув	Phe	Ser	Arg	Tyr	Pro	Asp	His		Lys	Gln	His	Asp		Phe
					805					810				_	815	
	Lys	Ser	Ala		Pro	Glu	Gly	Tyr		Gln	Glu	Arg	Thr	Ile	Phe	Phe
				820		_			825				_	830	~ 1	-1
30	Lys	Asp		Gly	Asn	Tyr	Lys		Arg	Ala	Glu	Val		Phe	GIU	GIŞ
			835		_	_	-1.	840	_	•	~ 3	- 1 -	845	Dh -	T	<i>α</i> 1
	Asp		Leu	Val	Asn	Arg		GIU	Leu	гàг	GIÀ		Asp	Phe	гуя	GIU
٠	D	850	7	т1.	T 011	C311	855	Tara	ĭ 011	C1.,	Th. 25	860	Tur	Asn	Cor	Hic
25	_	GIY	ASII	TTE	ьец	870	nis	гув	neu	Giu	875	ASII	ıyı	WPII	261	880
35	865	17-7	The same	Tla	Mot		Acn	Lare	Gln	Laze		Gly	Tle	Lys	Val	
	ASII	vai	ıyı	116	885	ALG	Asp	пуз	GIII	890	ASII	Gry	110	Dy S	895	
	Pho	Lare	Tla	Δνα		Δen	Tle	Glu	Aen		Ser	Val	Gln	Leu		Asp
	FILE	пуъ	110	900	1113	ASII	110	GIU	905	Gry	JCI	744	02	910		F
40	Hic	ጥህዮ	Gln		Asn	Thr	Pro	Tle		Asp	Glv	Pro	Val		Leu	Pro
70	1110	-7-	915	04				920			-		925			
	Asn	Asn		Tvr	Leu	Ser	Thr		Ser	Ala	Leu	Ser			Pro	Asn
		930		-1-			935					940	•	•		
			Arq	asp	His	Met		Leu	Leu	Glu	Phe	•	Thr	Ala	Ala	Gly
45	945	_	_	•		950					955					960
		Thr	Leu	Gly	Met	Asp	Glu	Leu	Tyr	Lys						
				-	965	_			-	970						
			(2) IN	FORM	ATIO	N FO	R SE	Q ID	NO:	68:					
50																
		,	2 \ C		NOT	CITAN	2 000	T T OF	TOO.							

- (i) SEQUENCE CHARACTERISTICS:
 - (A) LENGTH: 1788 base pairs
 - (B) TYPE: nucleic acid
 - (C) STRANDEDNESS: single
- 55 (D) TOPOLOGY: linear

150

(ii) MOLECULE TYPE: cDNA

(ix) FEATURE:

(A) NAME/KEY: Coding Sequence

(B) LOCATION: 1...1785

(D) OTHER INFORMATION:

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:68:

		(x	i) S	EQUE	NCE	DESC	RIPT	: NOI	SEQ	D	NO: 6	8:					
10					GCC Ala 5												48
15					GCC Ala												96
20					TAA neA												144
25					GGC Gly												192
25					CAC His												240
30	GTG Val	AAG Lys	CTA Leu	AAG Lys	CAG Gln 85	ATC Ile	GAG Glu	CAC His	ACT Thr	CTG Leu 90	AAT Asn	GAG Glu	AAG Lys	CGC Arg	ATC Ile 95	CTG Leu	288
35	CAG Gln	GCC Ala	GTC Vạl	AAC Asn 100	TTC Phe	CCG Pro	TTC Phe	CTG Leu	GTC Val 105	AAA Lys	CTT Leu	GAA Glu	TTC Phe	TCC Ser 110	TTC Phe	AAG Lys	336
40	Asp	Asn	Ser 115	Asn	Leu	Tyr	Met	Val 120	Met	Glu	Tyr	Val	Ala 125	Gly	Gly	GAG Glu	384
45	Met	Phe 130	Ser	His	Leu	Arg	Arg 135	Ile	Gly	Arg	Phe	Ser 140	Glu	Pro	His	GCC	432
	Arg 145	Phe	Tyr	Ala	Ala	Gln 150	Ile	Val	Leu	Thr	Phe 155	Glu	Tyr	Leu	His	Ser 160	480
50	Leu	Asp	Leu	Ile	Tyr 165	Arg	Asp	Leu	Lys	170	Glu	a Asn	Leu	Leu	11e	•	528
55	CAG Glr	CAG Gln	GGC	TAT Tyr 180	Ile	CAG Gln	GTG Val	ACA Thr	GAC Asp 185	Phe	GG7 Gly	r TTI / Phe	GCC Ala	AAG Lys 190	Arg	GTG Val	576

		GGC Gly															624
		ATT Ile 210															672
10		GGA Gly															720
15		GAC Asp															768
20	Arg	TTC Phe	Pro	Ser 260	His	Phe	Ser	Ser	Asp 265	Leu	Lys	Asp	Leu	Leu 270	Arg	Asn	816
25	Leu	CTG Leu	Gln 275	Val	Asp	Leu	Thr	Lys 280	Arg	Phe	Gly	Asn	Leu 285	Lys	Asp	Gly	.864
	Val	AAT Asn 290	Asp	Ile	Lys	Asn	His 295	Lys	Trp	Phe	Ala	Thr 300	Thr	Asp	Trp	Ile	912
30	Ala 305		Tyr	Gln	Arg	Lys 310	Val	Glu	Ala	Pró	Phe 315	Ile	Pro	Lys	Phe	Lys 320	960
35	Gly		Gly	Asp	Thr 325	Ser	Asn	Phe	Asp	Asp 330	Tyr	Glu	Glu	Glu	Glu 335	Ile	
40	Arg	GTC Val	Ser	11e 340	Asn	Glu	Lys	Сув	Gly 345	Lys	Glu	Phe	Thr	Glu 350	Phe	Gly	1056
45	Arg	Ala	Met 355	Ser	Lys	Gly	Glu	Glu 360	Leu	Phe	Thr	Gly	Val 365	Val	Pro		1104
	CTI	GTT Val 370	Glu	TTA Leu	GAT Asp	GGC Gly	GAT Asp 375	Val	' AAT Asn	GGG Gly	CAA Gln	AAA Lys 380	Phe	TCT Ser	GTT Val	AGT Ser	1152
50		, Glu					Ala					Leu				TTT Phe 400	1200
55						Lys					Tr					ACT Thr	1248

152

	ACT	CTC	ACT	TAT	GGT	GTT	CAA	TGC	TTT	TCT	AGA	TAC	CCA	GAT	CAT	ATG	1296
	Thr	Leu	Thr	Tyr	Gly	Val	Gln	Cys	Phe	Ser	Arg	Tyr	Pro	Asp	His	Met	
				420	_				425					430			
5																	
	AAA	CAG	CAT	GAC	TTT	TTC	AAG	AGT	GCC	ATG	CCC	GAA	GGT	TAT	GTA	CAG	1344
	Lys	Gln	His	Asp	Phe	Phe	Lys	Ser	Ala	Met	Pro	Glu	Gly	Tyr	Val	Gln	
	-		435					440					445				
10	GAA	AGA	ACT	ATA	TTT	TAC	AAA	GAT	GAC	GGG	AAC	TAC	AAG	ACA	CGT	GCT	1392
	Glu	Arg	Thr	Ile	Phe	.Tyr	Lys	Asp	Asp	Gly	Asn	Tyr	Lys	Thr	Arg	Ala	
		450					455					460					
		GTC															1440
15		Val	Lys	Phe	Glu		Asp	Thr	Leu	Val		Arg	IIe	GIu	Leu		
	465					470					475					480	
			~ m			<i>~</i> ~ ~ ~	C A III	003	n n a	8 MM	amm	ÓCA	C N C	ממת	א ידיר	CAA	1488
		ATT Ile															1400
20	GIY	TIE	Asp	Pile	ьуs 485	Giu	Asp	GIY	WPII	490	Deu	GIY	UTS	Lys	495	GIU	
20					405					490					473		
	тас	AAT	тат	AAC	TCA	CAT	ААТ	GTA	TAC	ATC	ATG	GCA	GAC	AAA	CCA	AAG	1536
		Asn															• •
	-1-		-2-	500					505				•	510		- -	
25																	
	AAT	GGC	ATC	AAA	GTT	AAC	TTC	AAA	ATT	AGÀ	CAC	AAC	ATT	AAA	GAT	GGA	1584
	Asn	Gly	Ile	Lys	Val	Asn	Phe	Lys	Ile	Arg	His	Asn	Ile	Lys	Asp	Gly	
			515					520					525				
30		GTT															1632
	Ser	Val	Gln	Leu	Ala	qaA	His	Tyr	Gln	Gln	Asn		Pro	Ile	Gly	Asp	
		530					535					540					
					-	993	~~~		G 3 M	m. 0	ama	maa	200		TO TO	CCC	1680
0.5		CCT															1000
35	-	Pro	vaı	ьeu	Leu		Asp	ASI	His	Tyr	555		THE	GIII	261	560	
	545					550					222					500	
	ىلىلى	TCC	ααα	САТ	CCC	AAC	GAA	AAG	AGA	GAT	CAC	ATG	ATC	CTT	CTT	GAG	1728
		Ser															
40	Dou		-1-	-104	565			/ -	5	570					575		
	TTT	GTA	ACA	GCT	GCT	GGG	ATT	AÇA	CAT	GGC	ATG	GAT	GAA	CTA	TAC	AAA	1776
		Val															
				580					585					590			
45						•											
	CCT	CAG	GAG	TAA													1788
	Pro	Gln															
			595														
50																	
			(2) IN	FORM	ATIO	и FO	R SE	Q ID	ио:	69:						
		,	٠, ٠	EO: IP	MOR	רונוא די	א טשט	DIO	T (7.0								
	,	(ICS:								
ce	-			מאש					cids								

152

(B) TYPE: amino acid(C) STRANDEDNESS: single

(D) TOPOLOGY: linear

(ii) MOLECULE TYPE: protein

(v) FRAGMENT TYPE: internal

5

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:69:

		(2	, .	1001	SIACE	DESC	JILLE J	LION.		, 10						
٠.,	Met 1	Gly	Asn	Ala	Ala 5	Ala	Ala	Lys	Lys	Gly 10	Ser	Glu	Gln	Glu	Ser 15	Val
10	Lys	Glu	Phe	Leu 20	Ala	Lys	Ala	Lys	Glu 25	Asp	Phe	Leu	Lys	Lys 30	Trp	Glu
	_		35			•		40					45		Ile	
15		50			_		55					60			His	
	65		•	•		70					75				Lys	80
		-			85					90					Ile 95	
20				100	•				105					110	Phe	
	_		115					120					125		Gly	
25		130					135					140			His His	
	145					150					155				Ile	160
30		_			165	_			•	170					175 Arg	
30				180					185					190		Pro
	-		195					200					205			Ala
35		210					215					220				Phe
	225	_				230		•			235				Lys	240
40					245					250					255	Asn
				260					265					270		Gly
	Val	Asn	275 Asp	Ile	Lys	Asn	His	280 Lys	Trp	Phe	Ala	Thr	285 Thr		Trp	Ile
45	Ala	290 Ile		Gln	Arg		295 Val		Ala			Ile		Lys	Phe	Lys
	305 Gly	Pro	Gly	Asp		310 Ser		Phe	Asp				Glu	Glu		320 Ile
50	Arg	Val	Ser		325 Asn	Glu	Lys	Cys				Phe	Thr			Gly
	Arg	Ala		340 Ser	Lys	Gly	Glu				Thr	Gly				Ile
cc	Leu			Leu	Asp	Gly				Gly	Gln				Val	Ser
55	Gly	370 Glu		Glu	Gly	Asp	375 Ala		туг	Gly	. Lys	380 Leu		Leu	Lys	Phe

	385					390					395					400		
	Ile	Cys	Thr	Thr	Gly 405	Lys	Leu	Pro	Val	Pro 410	Trp	Pro	Thr	Leu	Val 415	Thr		
5	Thr	Leu	Thr	Tyr 420	Gly	Val	Gln	Cys	Phe 425	Ser	Arg	Tyr	Pro	Asp 430	His	Met		
	Lys	Gln	His 435	Asp	Phe	Phe	Lys	Ser 440	Ala	Met	Pro	Glu	Gly 445	Tyr	Val	Gln		
	Glu	Arg 450	Thr	Ile	Phe	Tyr	Lys 455	Asp	Asp	Gly	Asn	Tyr 460	Lys	Thr	Arg	Ala		
10	465					470			•		475	Arg				480		
	_				485					490		Gly			495			
15	-			500					505		•	Ala		510				
			515					520				Asn	525					
		530					535	·. ·				Thr 540						
20	545					550					555	Ser				560		
		•			565					570		Met			575			
25				580	Ala	GIÀ	11e	Tnr	H1S 585	GIÀ	Met	Asp	GIU	ьец 590	Tyr	ьув		
	Pro	Gln	595										•					
30			(2)	IN	FORM	ATIOI	N FOI	R SE	Q ID	NO:	70:							
50		(:			NCE (٠				
			(B)	TYP	E: ni	ucle	ic a	cid										
35					OLOG			_	-									
		•		MOLE	CULE URE:	TYPI	E: cl	AMC										
40			(B)) Lo	ME/KI CATION HER	ON:	1:	2178	eque	nce	•							,
45		(:	xi) (SEQU	ENCE	DES	CRIP'	TION	: SE	Q ID	NO:	70:						
40												CTG						48
•	Met 1	ser	Asp	vaı	5 5	116	vai	ъув	GIU.	10	Trp	Leu	HIS	пуъ	15	Gry		
50																GAT Asp		96
55																CGT	:	144

E												TGC Cys 60					192	
5												CGC Arg					240	
10												ACT Thr					288	
15												GAC Asp					336	
20												TCA Ser					384	
25	TCA Ser	GGG Gly 130	GCT Ala	GAA Glu	GAG Glu	ATG Met	GAG Glu 135	GTG Val	TCC Ser	CTG Leu	GCC Ala	AAG Lys 140	CCC Pro	AAG Lys	CAC His	CGC Arg	432	
												CTG Leu					480	
30											Ala	ACA Thr				\mathtt{Tyr}	528	
35	GCC Ala	ATG Met	AAG Lys	ATC Ile 180	CTC Leu	AAG Lys	AAG Lys	GAA Glu	GTC Val 185	ATC Ile	GTG Val	GCC Ala	AAG Lys	GAC Asp 190	Glu	GTG Val	576	
40									Val			AAC Asn		Arg		Pro	624	
45	TTC Phe	CTC Leu 210	Thr	GCC Ala	CTG Leu	AAG Lys	TAC Tyr 215	TCT Ser	TTC Phe	CAG Glm	ACC Thr	CAC His	Asp	CGC	CTC Leu	TGC Cys	672	
45	TTT Phe 225	Val	ATG Met	GAG Glu	TAC	GCC Ala 230	Asn	GGG Gly	GGC Gly	GAG	CTC Lev 235	ı Phe	TTC Phe	CAC His	CTC Lev	TCC Ser 240	720	1
50	CGG	GAA J Glu	. CGT . Arg	GTG Val	TTC Phe 245	Ser	GAG Glu	GAC Asp	CGG Arg	GC0 Ala 250	a Arg	TTC Phe	TAT Tyr	GGC Gly	GCT / Ala 255	GAG Glu	768	}
55	ATT	GTG Val	TCA Ser	GCC Ala 260	Leu	GAC Asp	TAC Tyr	CTC Lev	CAC His 265	s Se	GAC	AAC 1 Lys	AA G	C GTC 270	l Va	TAC L Tyr	816	5

		GAC Asp															864
5		ATC Ile 290											Lys				912
10		ATG Met															960
15	CTG Leu	GAG Glu	GAC Asp	AAT Asn	GAC Asp 325	TAC Tyr	GGC Gly	CGT Arg	GCA Ala	GTG Val 330	GAC Asp	TGG Trp	TGG Trp	GGG Gly	CTG Leu 335	GGC Gly	1008
20		GTC Val															1056
25		CAT															1104
	CCG Pro	CGC Arg 370	Thr	CTT Leu	GGT Gly	CCC Pro	GAG Glu 375	GCC Ala	AAG Lys	TCC Ser	TTG Leu	CTT Leu 380	TCA	GGG Gly	CTG Leu	CTC	1152
30		AAG Lys															1200
35		ATC Ile															1248
40	TAC Tyr	GAG Glu	AAG Lys	AAG Lys 420	CTC Leu	AGC Ser	CCA Pro	CCC	TTC Phe 425	AAG Lys	CCC	CAG Gln	GTC Val	ACG Thr 430	TCG	GAG Glu	1296
45	ACT	GAC Asp	ACC Thr 435	Arg	TAT	TTT Phe	GAT Asp	GAG Glu 440	Glu	TTC	ACG	GCC Ala	CAG Gln 445	Met	ATC Ile	ACC Thr	1344
45	ATC Ile	ACA Thr	Pro	CCT Pro	GAC Asp	CAA Gln	GAT Asp 455	Asp	AGC Ser	ATG Met	GAC	TGT Cys 460	Val	GAC Asp	AGC Ser	GAG Glu	1392
50		g Arg					Gln					Ala				GCC Ala 480	1440
55						Ala					. Ly					TTC Phe	1488

		GGG Gly															1536
5		AAG Lys															1584
10	AAG Lys	CTG Leu 530															1632
15		CCC Pro					Thr										1680
20		TAC Tyr															1728
		GAA Glu															1776
25		TAC Tyr															1824
30	AAC Asn	CGC Arg 610	ATC Ile	GAG Glu	CTG Leu	AAG Lys	GGC Gly 615	ATC Ile	GAC Asp	TTC Phe	AAG Lys	GAG Glu 620	GAC Asp	GGC Gly	AAC Asn	ATC Ile	1872
35		GGG Gly										His					1920
40		GCC Ala															1968
					Asp										Gln	CAG Gln	2016
45				Ile					Val					Asn		TAC Tyr	2064
50			Thr					Ser					Glu			GAT Asp	2112
55		Met					Phe					Gly				GGC Gly 720	2160

ATG GAC GAG CTG TAC AAG TAA 2181 Met Asp Glu Leu Tyr Lys 725 5 (2) INFORMATION FOR SEQ ID NO:71: (i) SEQUENCE CHARACTERISTICS: 10

- (A) LENGTH: 726 amino acids
- (B) TYPE: amino acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear
- (ii) MOLECULE TYPE: protein 15 (v) FRAGMENT TYPE: internal
 - (xi) SEQUENCE DESCRIPTION: SEQ ID NO:71:

20 Met Ser Asp Val Ala Ile Val Lys Glu Gly Trp Leu His Lys Arg Gly Glu Tyr Ile Lys Thr Trp Arg Pro Arg Tyr Phe Leu Leu Lys Asn Asp Gly Thr Phe Ile Gly Tyr Lys Glu Arg Pro Gln Asp Val Asp Gln Arg 25 Glu Ala Pro Leu Asn Asn Phe Ser Val Ala Gln Cys Gln Leu Met Lys 55 Thr Glu Arg Pro Arg Pro Asn Thr Phe Ile Ile Arg Cys Leu Gln Trp 75 30 Thr Thr Val Ile Glu Arg Thr Phe His Val Glu Thr Pro Glu Glu Arg 90 Glu Glu Trp Thr Thr Ala Ile Gln Thr Val Ala Asp Gly Leu Lys Lys 105 Gln Glu Glu Glu Met Asp Phe Arg Ser Gly Ser Pro Ser Asp Asn 35 120 Ser Gly Ala Glu Glu Met Glu Val Ser Leu Ala Lys Pro Lys His Arg · 135 Val Thr Met Asn Glu Phe Glu Tyr Leu Lys Leu Leu Gly Lys Gly Thr 150 155 40 Phe Gly Lys Val Ile Leu Val Lys Glu Lys Ala Thr Gly Arg Tyr Tyr 165 170 Ala Met Lys Ile Leu Lys Lys Glu Val Ile Val Ala Lys Asp Glu Val 185 Ala His Thr Leu Thr Glu Asn Arg Val Leu Gln Asn Ser Arg His Pro 45 200 Phe Leu Thr Ala Leu Lys Tyr Ser Phe Gln Thr His Asp Arg Leu Cys 215 Phe Val Met Glu Tyr Ala Asn Gly Gly Glu Leu Phe Phe His Leu Ser 230 235 50 Arg Glu Arg Val Phe Ser Glu Asp Arg Ala Arg Phe Tyr Gly Ala Glu 245 250 Ile Val Ser Ala Leu Asp Tyr Leu His Ser Glu Lys Asn Val Val Tyr 265 Arg Asp Leu Lys Leu Glu Asn Leu Met Leu Asp Lys Asp Gly His Ile 55 280 Lys Ile Thr Asp Phe Gly Leu Cys Lys Glu Gly Ile Lys Asp Gly Ala

		290					295					300				
	Thr 305		Lys	Thr	Phe	Cys 310		Thr	Pro	Glu	Tyr 315		Ala	Pro	Glu	Val 320
5		Glu	Asp	Asn	Asp 325	Tyr	Gly	Arg	Ala	Val 330	Asp	Trp	Trp	_	Leu 335	Gly
	Val	Val	Met	Tyr 340	Glu	Met	Met	Cys	Gly 345	Arg	Leu	Pro	Phe	Tyr 350	Asn	Gln
•	Asp	His	Glu 355	Lys	Leu	Phe	Glu	Leu 360	Ile	Leu	Met	Glu	Glu 365	Ile	Arg	Phe
10	Pro	Arg 370	Thr	Leu	.Gly	Pro	Glu 375	Ala	Lys	Ser	Leu	Leu 380	Ser	Gly	Leu	Leu
	385	_			Lys	390			-	_	395			_		400
15					His 405	_				410			_		415	
	•		_	420	Leu				425					430		
		_	435		Tyr		_	440					445			
20		450		·	Asp		455	-				460		_		
	465	_			Phe Val	470				_	475					480
25		_			485 Pro					490	_	_			495	
		_		500	Val				505		-	_	_	510		
30		_	515		Lys		_	520					525			
	Trp	530					535					540				
	545 Arg					550				-	555					560
35		<u>.</u>			565 Val		_			570					575	
	Asn	Tyr	Lys	580 Thr	Arg	Ala	Glu	Val	585 Lys	Phe	Glu	Gly	Asp	590 Thr	Leu	Val
40	Asn	Arg	595 Ile	Glu	Leu	Lys	Gly	600 Ile	Asp	Phe	Lys	Glu	Asp	Gly	Asn	Ile
		610 Gly	His	Lys	Leu		615 Tyr	Asn	Tyr	Asn		620 His	Asn	Val	Tyr	Ile
45	625 Met	Ala	Asp	Lys		630 Lys	Asn	Gly	Ile	_		Asn	Phe	Lys		640 Arg
45	His	Asn	Ile	Glu 660	645 Asp	Gly	Ser	Val	Gln 665	650 Leu		Asp	His	Tyr 670	655 Gln	Gln
	Asn	Thr	Pro 675		Gly	Asp	Gly	Pro 680		Leu	Leu	Pro	Asp 685	Asn	His	Tyr
50	Leu	Ser 690	Thr	Gln	Ser	Ala	Leu 695		Lys	Asp	Pro	Asn 700			Arg	Asp
	His 705			Leu	Leu	Glu 710		Val	Thr	Ala	Ala 715		Ile	Thr	Leu	Gly 720
55	Met	Asp	Glu	Leu	Tyr 725	Lys										

145

55

160

										100							
			(2)	INE	ORMA	MOITA	FOF	SEC] ID	NO:7	2:						
5		i)	(A) (B) (C)	EQUEN LENC TYPI STRA	ETH: E: nu ANDEI	2751 iclei NESS	bas c ac	se pa sid ingle	irs					•		·	
10		•		OLEC FEATU		TYPE	E: cI	ANC							•	. *	
15			(B)	NAM LOC OTI	CATIO	N: 1	2	2748	equer	ice						٠.	
		()	(i) S	EQUI	ENCE	DESC	RIPT	: NOI	SEC) ID	NO: 7	72:					
20												GCG Ala					48
												CAG Gln					. 96
25												TTC Phe					144
30		-										TTT Phe 60					192
35												AAG Lys					240
40												GGA Gly					288
45												ACA Thr					336
.5												GGA Gly					384
50	GGG	ATG	AAA	TGT	GAC	ACC	TGC	GAC	ATG	AAT	GTT	CAC	AAC	CAG	TGT	GTG	432

160

480

160

Gly Met Lys Cys Asp Thr Cys Asp Met Asn Val His Asn Gln Cys Val

ATC AAT GAC CCT AGC CTC TGC GGA ATG GAT CAC ACA GAG AAG AGG GGG

Ile Asn Asp Pro Ser Leu Cys Gly Met Asp His Thr Glu Lys Arg Gly

140

								•									
					Lys					Asp					GTC Val		528
_					165					170					175		
5																	
															CTT		 576
	Val	Arg	Asp	A1a 180	Lys	Asn	Leu	Ile	Pro 185	Met	Asp	Pro	Asn	190	Leu	ser	
10	ርአጥ	ССТ	יימיי	GTG	אמ	CTG	מממ	רדים	איזיכי	ССТ	GAC	CCC	ממ	דעע	GAG	AGC	624
10															Glu		021
	rop	710	195	741	272	Deu	275	200	110		м		205		-		
	AAA	CAG	AAA	ACC	AAA	ACC	ATC	CGC	TCC	AAC	CTG	AAT	CCT	CAG	TGG	AAT	672
15	Lys	Gln 210	rys	Thr	Lys	Thr	Ile 215	Arg	Ser	Asn	Leu	Asn 220	Pro	Gln	Trp	Asn	
	GAG	TCC	TTC	ACG	TTC	AAA.	тта	AAA	CCT	TCA	GAC	AAA	GAC	CGG	CGA	CTG	720
															Arg	_	
20	225	-				230		1-			235		•		J	240	
	TCT	GTA	GAA	ATC	TGG	GAC	TGG	GAT	CGG	ACG	ACT	CGG	TAA	GAC	TTC	ATG	768
	Ser	Val	Glu	Ile	Trp	qaA	Trp.	Asp	Arg	Thr	Thr	Arg	Asn	Asp	Phe	Met	
					245					250					255		
25															~~~		
															GCC		816
	GIY	ser	Leu	260	Pne	GIÀ	vaı	ser	265	Leu	Met	гув	Met	270	Ala	Sei	
30	GGA	TGG	TAT	AAA	GCT	CAC	AAC	CAA	GAA	GAG	GGC	GAA	TAT	TAC	AAC	GTG	864
															Asn	_	
			275					280					285				•
															CAG		912
35	Pro	Ile 290	Pro	Glu	Gly	Asp	Glu 295	Glu	Gly	Asn	Met	Glu 300	Leu	Arg	Gln	Lys	
	יויידיידי	GAG	AAA	GCC	AAG	СТА	GGT	CCT	GTT	GGT	AAC	AAA	GTC	ATC	AGC	CCT	960
															Ser		
40	305					310	,			2	315	-,-				320	
															AAA		1008
	Ser	Glu	Asp	Arg	Lys	Gln	Pro	Ser	Asn	Asn	Leu	Asp	Arg	Val	Lys	Leu	
					325					330					335		
45																	
															GGG		1056
	Thr	Asp	Phe		Phe	Leu	Met	Val		Gly	Lys	Gly	Ser		Gly	Lys	
				340					345					350			
. 50															3.00	220	1104
50															ATC		1104
	val	Met		Ala	Asp	Arg	гàг		Thr	Glu	Glu	ьeu		ата	Ile	пÀг	
			355					360					365				
	א מונים	CITIC	א א מ	אאר	C N C	CITIC	OMO	אשמ	0×0	020	CNC	CAC	Guc	G N C	ייים	ACC	1152
55																Thr	
55	116	370	пλр	פעה	nap	Val	375	116	GT11	чер	vah	380		GIU	Cys		
		5,0					5/3					200					

5		AAG Lys										1200
Ü		CAC His										1248
10	 	 GTC Val 420			 							1296
15		AAG Lys										1344
20		TTC Phe										1392
25		AAT Asn										1440
	 	ATG Met										1488
30		GGA Gly 500										1536
35		GGG Gly										1584
40		CTA Leu										1632
45		CAG Gln								Lys	_	1680
		GAA Glu					Gly					1728
50		CGA Arg 580	Leu			Glu				Val	AGA Arg	1776
55		TTC Phe			Asp				Glu		AGG Arg	1824

AAC TTT GAC AAG TTC TTC ACG CGA GGA CAG CCT GTC TTA ACA CCA CCA Asn Phe Asp Lys Phe Phe Thr Arg Gly Gln Pro Val Leu Thr Pro Pro 625 630 635 640 10 GAT CAG CTG GTC ATT GCT AAC ATA GAC CAA TCT GAT TTT GAA GGG TTC Asp Gln Leu Val Ile Ala Asn Ile Asp Gln Ser Asp Phe Glu Gly Phe 645 650 655 TCG TAT GTC AAC CCC CAG TTT GTG CAC CCA ATC TTG CAA AGT GCA GTA 15 Ser Tyr Val Asn Pro Gln Phe Val His Pro Ile Leu Gln Ser Ala Val 660 665 670 GGG CGC GCC ATG AGT AAA GGA GAA GAA CTT TTC ACT GGA GTT GTC CCA	68
Asn Phe Asp Lys Phe Phe Thr Arg Gly Gln Pro Val Leu Thr Pro Pro 625 630 635 640 10 GAT CAG CTG GTC ATT GCT AAC ATA GAC CAA TCT GAT TTT GAA GGG TTC Asp Gln Leu Val Ile Ala Asn Ile Asp Gln Ser Asp Phe Glu Gly Phe 645 650 655 TCG TAT GTC AAC CCC CAG TTT GTG CAC CCA ATC TTG CAA AGT GCA GTA Ser Tyr Val Asn Pro Gln Phe Val His Pro Ile Leu Gln Ser Ala Val 660 665 670	68
625 630 635 640 10 GAT CAG CTG GTC ATT GCT AAC ATA GAC CAA TCT GAT TTT GAA GGG TTC Asp Gln Leu Val Ile Ala Asn Ile Asp Gln Ser Asp Phe Glu Gly Phe 645 TCG TAT GTC AAC CCC CAG TTT GTG CAC CCA ATC TTG CAA AGT GCA GTA Ser Tyr Val Asn Pro Gln Phe Val His Pro Ile Leu Gln Ser Ala Val 660 665 670	
10 GAT CAG CTG GTC ATT GCT AAC ATA GAC CAA TCT GAT TTT GAA GGG TTC Asp Gln Leu Val Ile Ala Asn Ile Asp Gln Ser Asp Phe Glu Gly Phe 645 TCG TAT GTC AAC CCC CAG TTT GTG CAC CCA ATC TTG CAA AGT GCA GTA Ser Tyr Val Asn Pro Gln Phe Val His Pro Ile Leu Gln Ser Ala Val 660 665 20	
Asp Gln Leu Val Ile Ala Asn Ile Asp Gln Ser Asp Phe Glu Gly Phe 645 TCG TAT GTC AAC CCC CAG TTT GTG CAC CCA ATC TTG CAA AGT GCA GTA Ser Tyr Val Asn Pro Gln Phe Val His Pro Ile Leu Gln Ser Ala Val 660 665 670	
TCG TAT GTC AAC CCC CAG TTT GTG CAC CCA ATC TTG CAA AGT GCA GTA 20 15 Ser Tyr Val Asn Pro Gln Phe Val His Pro Ile Leu Gln Ser Ala Val 660 665 670	16
TCG TAT GTC AAC CCC CAG TTT GTG CAC CCA ATC TTG CAA AGT GCA GTA 20 15 Ser Tyr Val Asn Pro Gln Phe Val His Pro Ile Leu Gln Ser Ala Val 660 665 670	16
15 Ser Tyr Val Asn Pro Gln Phe Val His Pro Ile Leu Gln Ser Ala Val 660 665 670	16
15 Ser Tyr Val Asn Pro Gln Phe Val His Pro Ile Leu Gln Ser Ala Val 660 665 670	16
660 665 670	
GGG CGC GCC ATG AGT AAA GGA GAA GAA CTT TTC ACT GGA GTT GTC CCA 20	
	64
Gly Arg Ala Met Ser Lys Gly Glu Glu Leu Phe Thr Gly Val Val Pro	-
20 675 680 685	
ATT CTT GTT GAA TTA GAT GGC GAT GTT AAT GGG CAA AAA TTC TCT GTT 21	12
Ile Leu Val Glu Leu Asp Gly Asp Val Asn Gly Gln Lys Phe Ser Val	
690 695 700	
25 .	
	60
Ser Gly Glu Gly Glu Gly Asp Ala Thr Tyr Gly Lys Leu Thr Leu Lys	,
705 710 715 720	
30 TTT ATT TGC ACT ACT GGG AAG CTA CCT GTT CCA TGG CCA ACG CTT GTC 22	08
Phe Ile Cys Thr Thr Gly Lys Leu Pro Val Pro Trp Pro Thr Leu Val	
725 730 735	
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MCI fiel did fiel and did did fiel and fiel and did and	56
35 Thr Thr Leu Thr Tyr Gly Val Gln Cys Phe Ser Arg Tyr Pro Asp His	
740 745 750	
22 222 C1G C1M C1G MMM MMG 21G 1GM CCG 1MG CCG C11 CCM M1M CM1	0.4
11.0 11.1 01.0 01.1 01.0 11.0 11.0 10.1 000 11.0 000 11.0	04
Met Lys Gln His Asp Phe Phe Lys Ser Ala Met Pro Glu Gly Tyr Val 40 755 760 765	
40 755 760 765	
CAG GAA AGA ACT ATA TTT TAC AAA GAT GAC GGG AAC TAC AAG ACA CGT 23	52
Gln Glu Arg Thr Ile Phe Tyr Lys Asp Asp Gly Asn Tyr Lys Thr Arg	
770 775 780	
45	
001 011 010 1110 1110 011 0110 011 012 013	100
Ala Glu Val Lys Phe Glu Gly Asp Thr Leu Val Asn Arg Ile Glu Leu	
785 790 795 800	
50 - 333 GGM 3MM G3M MMM 333 G33 G3M GGS 33G 3MM GMM GGA G3G 333 AMG 97	148
OU THE COL THE CHE CHE CHE COLL THE COLL THE COLL THE COLL THE CHE CHE CHE CHE CHE CHE CHE CHE CHE C	120
Lys Gly Ile Asp Phe Lys Glu Asp Gly Asn Ile Leu Gly His Lys Met 805 810 815	
503	
GAA TAC AAT TAT AAC TCA CAT AAT GTA TAC ATC ATG GCA GAC AAA CCA 24	196
55 Glu Tyr Asn Tyr Asn Ser His Asn Val Tyr Ile Met Ala Asp Lys Pro	
820 825 830	

		AAT Asn															2544
5																	
	GGA	AGC	GTT	CAA	TTA	GCA	GAC	CAT	TAT	CAA	CAA	AAT	ACT	CCA	ATT	GGC	2592
	Gly	Ser	Val	Gln	Leu	Ala	Asp	His	Tyr	Gln	Gln	Asn	Thr	Pro	Ile	Gly	
		850					855				•	860					
10		GGC															2640
	Asp	Gly	Pro	Val	Leu	Leu	Pro	Asp	Asn	His	_	Leu	Ser	Thr	Gln		
	865					870					875					880	
			maa		a.m						~~~	~~~	7 m.c	1 ma	OMM:	OTTO:	2600
45		CTT															2688
15	Ala	Leu	ser	гÀг	885	Pro	Asn	GIU	гув	890	Авр	HIS	Met	TTE	895	Leu	
					883					090					095		
	GAG	TTT	СТА	ACA	GCT	GCT	GGG	ΆͲͲ	ACA	CAT	GGC	ATG	GAT	GAA	CTA	TAC	2736
		Phe															
20	014			900			1		905		1		<u>-</u>	910		4	
																•	
	AAA	CCT	CAG	GAG	TAA												2751
	Lys	Pro	Gln	Glu													
•			915		*											•	
25																	
			(2)) IN	FORM	OITA	N FOI	R SE	ם ב	NO:	/3:						
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35		(:	ii) ľ	MOLE	CULE	TYPI	E: p:	rote	in								
		7)	/) FI	RAGM	ENT :	TYPE	: in	tern	al								
		(2	ki) S	SEQU	ENCE	DES	CRIP'	TION	: SE	Q ID	NO:	73:					
40	Met	Ala	Asp	Val	Tyr	Pro	Ala	Asn	qaA		Thr	Ala	Ser	Gln		Val	
	1				5			_	_	10			_		15		
	Ala	Asn	Arg		Ala	Arg	Lys	Gly		Leu	Arg	Gln	Lys		Val	His	
			_	20		_	_,		25	_	-1	m1	•	30	D	mb ee	
45	GIu	vaı		Asp	His	ràs	Phe		Ala	Arg	Pne	Pne		GIN	Pro	Thr	
45	Dh.a	0	35	774 -	0	mb se	7	40	T1.	Therm	C1	Dho	45	Lare	Gln	Clv	
	Pne	Cys 50	ser	HIS	Cys	The	Авр 55	Pne	TIE	TIP	GIY	60	GTÀ	пур	GIII	Gly	
	Dho		Cvc	Gla	t/all	Cve		Dho	Val	บรา	uic		Ara	Cve	His	Glu	•
	65	זוגט	Cys	GAII	val	70	Cys	FIIG	vai	val	75	n y o	ar 9	-ys	-110	80	
50		Val	Thr	Phe	Ser		Pro	Glv	Δla	Asn		GI v	Pro	Asp	Thr	Asp	
00	File	- 41	-111	- 110	85	-13	-10	Jry	.,,4	90	-13	1			95		
	Asp	Pro	Ara	Ser		His	Lvs	Phe	Lvs		His	Thr	Tvr	Glv		Pro	•
			3	100	1-		, -	- ***	105				-7-	110		-	
	Thr	Phe	Сув		His	Cys	Gly	Ser		Leu	Tyr	Gly	Leu	Ile	His	Gln	
55			115	•		-	- 4	120			•	•	125				
	Gly	Met	Lys	Cys	Asp	Thr	Cys	Asp	Met	Asn	Val	His	Asn	Gln	Сув	. Val	

		130					135					140				
	Ile 145	Asn	Asp	Pro	Ser	Leu 150	Сув	Gly	Met	Asp	His 155	Thr	Glu	Lys	Arg	Gly 160
5			_		165					170				His	175	
		_	-	180					185	•				Gly 190		
	-		195					200					205	Asn		
10	-	210					215					220		Gln		
	225					230					235			Arg		240
15			•		245					250				Asp	255	
	-	•		260					265					270 Tyr		
20	_		275					280				•	285	Arg		
		290					295					300		Ile		
•	305		•		-	310	_			_	315	_		Val		320
25	Thr	Asp	Phe	Asn	325 Phe	Leu	Met	Val	Leu	330 Gly	Lys	Gly	Ser	Phe	335 Gly	Lys
	Val	Met	Leu	340 Ala	Asp	Arg	Lys	Gly	345 Thr	Glu	Glu	Leu		350 Ala	Ile	Lys
30	Ile		355 Lys	Lys	Asp	Val		360 Ile	Gln	Asp	Asp		365 Val	Glu	Cys	Thr
		370 Val	Glu	Lys	Arg	Val 390	375 Leu	Ala	Leu	Leu	Asp 395	780 780	Pro	Pro	Phe	Leu 400
35	385 Thr	Gln	Leu	His	Ser		Phe	Gln	Thr	Val 410	Asp	Arg	Leu	Tyr	Phe	
33	Met	Glu	Tyr	Val 420		Gly ·	Gly	Asp	Leu 425	Met		His	Ile	Gln 430		Val
	Gly			Lys					Val	Phe	Tyr		Ala 445	Glu	Ile	Ser
40	Ile	Gly 450	Leu	Phe	Phe	Leu	His 455	_	Arg	Gly	Ile	Ile 460	Tyr	Arg	Asp	Leu
	465					470					475					Ala 480
45					485					490					495	Arg
				500					505					510		Tyr
			515					520					525			Leu
50	_	530					535					540				Asp
	545					550					555					Ser 560
55					565					570	1				575	Gln
	FIO	La T C	ت ر ب	9		· · · · · · · · · · · · · · · · · · · ·	~y =	· · · · y			y		=	,		3

				580					585					590		
	Glu	His	Ala 595		Phe	Arg	Arg	Ile 600		Trp	Glu	Lys	Leu 605	Glu	Asn	Arg
5	Glu	Ile 610	Gln	Pro	Pro	Phe	Lys 615	Pro	Lys	Val	сув	Gly 620	Lys	Gly	Ala	Glu
	Asn 625	Phe	Asp	Lys	Phe	Phe 630	Thr	Arg	Gly	Gln	Pro 635	Val	Leu	Thr	Pro	Pro 640
		Gln	Leu	Val	Ile 645	Ala	Asn	Ile	Asp	Gln 650	Ser	Asp	Phe	Glu	Gly 655	Phe
10	Ser	Tyr	Val	Asn 660	Pro	Gln	Phe	Val	His 665	Pro	Ile	Leu	Gln	Ser 670	Ala	Val
	-	_	Ala 675					680					685			
15		690					695					700				
	705	_	Glu			710					715					720
	·		Cys		725			•	·	730					735	
20			Leu	740					745	•				750		
			Gln 755					760					765			
25		770	Arg				775					780				
	785		Val			790					795					800
	_	•	Ile		805					810					815	
30			Asn	820					825					830		
	_		Gly 835					840					845			
35	_	850	Val				855					860				
	865		Pro			870					875					880
			Ser		885	•				890					895	
40			Val	900		Ala	GIY	11e	905		GIY	мес	Абр	910		Tyr
	Lys	Pro	Gln 915	GIu												
45			(2)) IN	FORM	ATIO	N FO	R SE	Q ID	NO:	74:					
		(i) Si			CHAR 215										
						ucle		_								
50						DNES			e			•				
						Y: 1		-								

(D) TOPOLOGY: linear

- (ii) MOLECULE TYPE: cDNA
- (ix) FEATURE:

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(A) NAME/KEY: Coding Sequence

(B) LOCATION: 1...2154(D) OTHER INFORMATION:

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:74:

		()	ci) S	EQUE	ENCE	DESC	RIPI	: NOI:	SEC) ID	NO:	74:					
5						~~~									ama	ama.	4.0
												GTG					48
		Ser	ser	TTE	_	Pro	Pne	Thr	Pro		vaı	Val	гÀг	Arg		ren	
	1				5					10					15		
10	CCA	тсс	מממ	ממ	тса	CCT	CCT	GGG	тст	GGD	GGA	GCA	GGC	GGA	GGA	GAG	96
10												Ala					
	O _T		-7-	20			,	,	25	,	1		1	30	2		
				_ •													
	CAG	TAA	GGG	CAG	GAA	GAA	AAG	TGG	TGT	GAG	AAA	GCA	GTG	AAA	AGT	CTG	144
15	Gln	Asn	Gly	Gln	Glu	Glu	Lys	Trp	Cys	Glu	Lys	Ala	Val	Lys	Ser	Leu	
			35					40					45				
				•													
												GAG					192
	Val	_	ГÄг	Leu	Lys	rys		GIA	Arg	Leu	Asp	Glu	Leu	GIU	гàв	Ala	
20	•	50					55					60					
	አጥር ⁻	אככ	אכידי	ממי	ממ	тст	דממ	אריזי	מממ	тст	CTT	ACC	ΔΤΔ	CCA	AGC	ACT	240
												Thr					
	65					70			-10	-7-	75					80	
25																	
	TGC	TCT	GAA	ATT	TGG	GGA	CTG	AGT	ACA	CCA	AAT	ACG	ATA	GAT	CAG	TGG	288
	Cys	Ser	Glu	Ile	Trp	Gly	Leu	Ser	Thr	Pro	Asn	Thr	Ile	Asp	Gln	Trp	
					85					90					95		
																	226
30												ACC					336
	Asp	Thr	Thr	_	Leu	Tyr	ser	Pne		GIU	GIN	Thr	Arg		Leu	Asp	
				100					105				•	110			•
	CCT	ССТ	СТС	CAG	атъ	TCC	СДТ	CGA	444	CCA	ጥፐር	CCA	САТ	GTT	ATA	TAT	384
35												Pro					
00	U -1	5	115					120	-1-	1			125			-	
	TGC	CGA	TTA	TGG	CGC	TGG	CCT	GAT	CTT	CAC	AGT	CAT	CAT	GAA	CTC	AAG	432
	Cys	Arg	Leu	Trp	Arg	Trp	Pro	qaA	Leu	His	Ser	His	His	Glu	Leu	Lys	
40		130					135					140					
																	400
												AAA					480
		He	Glu	Asn	Cys		Tyr	Ala	Pne	Asn		Lys	ьуѕ	Asp	GIU	160	
45	145					150					155					100	
40	ጥርሞ	GTA	מממ	ССТ	ጥልሮ	CAC	ייימיי	CAG	DCD.	תייים	GAG	ACA	CCA	GTT	TTG	CCT	528
												Thr					
	٠, ٥				165		-1-		5	170					175		
50	CCA	GTA	TTA	GTG	CCC	CGA	CAC	ACC	GAG	ATC	CTA	ACA	GAA	CTT	CCG	CCT	576
	Pro	Val	Leu	Val	Pro	Arg	His	Thr	Glu	Ile	Leu	Thr	Glu	Leu	Pro	Pro	
				180					185					190			
												<u>.</u>					
																GCA	624
55	Leu	Asp		Tyr	Thr	His	Ser		Pro	Glu	Asn	Thr			Pro	Ala	
			195					200					205				

						•				
5						ACG Thr 220				672
J						CAG Gln			AGT Ser 240	720
10						ACT Thr				768
15						TAC Tyr				816
20						CAG Gln				864
25						GAT Asp 300				912
						CTC Leu				960
30						ATA Ile				1008
35						GAG Glu			GAT Asp	1056
40						CAG Gln				1104
						TGT Cys 380				1152
45						CAG Gln				1200
50						TGC Cys				1248
55						AGG Arg		Val		1296

														CTA Leu			1344
5			100														
J	ттс	GAC	ααα	GTA	тта	ACT	CAG	ATG	GGA	TCC	ССТ	TCA	GTG	CGT	TGC	TCA	1392
														Arg			
	ДСи	450	_,,	• • • •			455		U -1	502		460			- 1		
		450					433					400					
40	300	3 mg	max.	maa	מיייא	ccc	ccc	ccc	ccc	CAT	CCN	ccc	OTC.	GCC	אככ	እጥር!	1440
10																	1440
		Met	Ser	пр	val		Arg	MIG	Arg	Авр		PIO	ATT	Ala	1111		
	465					470					475					480	
				~~~	~~~	~~~	ama						~~~	* ma	ama	ama	1400
														ATC		_	1488
15	Val	Ser	гÀг	GIA		GIU	ren	Pne	Thr	_	vaı	vaı	Pro	Ile		var	·
					485					490					495		
														TCC	_	_	1536
	Glu	Leu	Asp	_	_	vaı	Asn	GIA		Lys	Pne	ser	vaı	Ser	GIY	GIU	
. 20				500					505					510			
																	2504
														TTC			1584
	Gly	Glu	-	Asp	Ala	Thr	Tyr	-	Lys	Leu	Thr	Leu	-	Phe	Ile	Cys	
			515					520					525				
25																	
														ACC			1632
	Thr	Thr	Gly	Lys	Leu	Pro	Val	Pro	Trp	Pro	Thr	Leu	Val	Thr	Thr	Leu	
		530					535					540					
30														ATG		_	1680
	Thr	Tyr	Gly	Val	Gln	Cys	Phe	Ser	Arg	Tyr	Pro	Asp	His	Met	ГÀв		
	545					550					555					560	•
														CAG			1728
35	His	Asp	Phe	Phe	Lys	Ser	Ala	Met	Pro	Glu	Gly	Tyr	Val	Gln	Glu	Arg	
					565					570					575		
	ACC	ATC	TTC	TTC	AAG	GAC	GAC	GGC	AAC	TAC	AAG	ACC	CGC	GCC	GAG	GTG	1776
	Thr	Ile	Phe	Phe	Lys	Asp	Asp	Gly	Asn	Tyr	Lys	Thr	Arg	Ala	Glu	Val	
40				580					585					590			
	AAG	TTC	GAG	GGC	GAC	ACC	CTG	GTG	AAC	CGC	ATC	GAG	CTG	AAG	GGC	ATC	1824
	Lys	Phe	Glu	Gly	Asp	Thr	Leu	Val	Asn	Arg	Ile	Glu	Leu	Lys	Gly	Ile	
	-		595					600					605				
45	•																
	GAC	TTC	AAG	GAG	GAC	GGC	AAC	ATC	CTG	GGG	CAC	AAG	CTG	GAG	TAC	AAC	1872
	Asp	Phe	Lys	Glu	Asp	Gly	Asn	Ile	Leu	Gly	His	Lys	Leu	Glu	Tyr	Asn	
	-	610	-		_	_	615			•		620					
50	TAC	AAC	AGC	CAC	AAC	GTC	TAT	ATC	ATG	GCC	GAC	AAG	CAG	AAG	AAC	GGC	1920
																Gly	
	625					630	, _				635			•		640	
	ATC	AAG	GTG	AAC	TTC	AAG	ATC	CGC	CAC	AAC	ATC	GAG	GAC	GGC	AGC	GTG	1968
55														Gly			
-		-,, 5			645	-1-		3		650				1	655		
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															GGC Gly		2016
5																	
	GTG	CTG	CTG	CCC	GAC	AAC	CAC	TAC	CTG	AGC	ACC	CAG	TCC	GCC	CTG	AGC	2064
	Val	Leu	Leu	Pro	Asp	Asn	His	Tyr	Leu	Ser	Thr	Gln	Ser	Ala	Leu	Ser	
			675					680					685				
10															TTC		2112
	Lys		Pro	Asn	Glu	Lys		Asp	His	Met	Val		Leu	Glu	Phe	Val	
		690					695				•	700					
			~~~	~~~			~~~	~~~		a. a	~~~	omo	m » «	220	m 3 3	•	2157
45															TAA		2157
15		Ala	Ата	GTÅ	116	Thr	Leu	GIÀ	Met	Asp		neu	TAL	пåе			
	705					710					715						
																	•
			(2)	TNE	ORMA	ATION	J FOI	SEC	OTD	NO: 7	5:						
20			(2)	1111	014.11			,	2 10		٠.						
20		(:	L) SI	OUE	ICE (CHARA	ACTE	RIST	ICS:								
			•	_		718								•			
						nino										•	
						ONES			9		•						
25						Y: 1:		_									•
			•							•							
		(:	ii) M	OLE	CULE	TYPI	E: p:	rote:	in								
		(7	J) FI	RAGMI	ENT :	TYPE	: in	terna	al								
30		()	ci) S	EQUE	ENCE	DES	CRIP'	гіои	: SE	O ID	NO: 7	75 :					
			_			_				_			_	_	•	•	
		Ser	Ser	Ile		Pro	Phe	Thr	Pro		Val	Val	ГÀв	Arg	Leu	Leu	
	1	_			5		01	~ 1		10	03.	27-	a 1	σ1	15	G 3.1	
0.5	GIA	Trp	гàг		ser	АТА	GIĀ	GIY		GIA	GIA	ATA	GIY		Gly	GIU	
35	a 1	3	a1	20	a1	a 1	T	(17)	25	~1	T		17 a l	30	Car	T.611	
	GIN	Asn	35	GIN	GIU	GIU	гÀв	11p	Cys	GIU	гуѕ	Ala	45	пур	Ser	пец	
	17-1	T 170		Lou	Two	Tara	Thr		7~~	Lou	A cro	Glu		Glu	Lys	Δla	
	val	ப்த 50	пув	пеп	гув	пур	55	Gly	Arg	Deu	web	GIU	пец	GIU	Ly S	niu	
40	Tle						J J					60					
40		Thr	Thr	Gln	Δen	Cve		Thr	Lve	Cve	Val	60 Thr	Tle	Pro	Ser	Thr	
		Thr	Thr	Gln	Asn			Thr	Lys	Cys			Ile	Pro	Ser		
	65					70	Asn		_		75	Thr				80	
	65				Trp	70	Asn		_	Pro	75	Thr			Gln	80	
	65 Cys	Ser	Glu	Ile	Trp	70 Gly	Asn Leu	Ser	Thr	Pro 90	75 Asn	Thr Thr	Ile	Asp	Gln 95	80 Trp	
45	65 Cys	Ser	Glu	Ile Gly	Trp	70 Gly	Asn Leu	Ser	Thr	Pro 90	75 Asn	Thr Thr	Ile	Asp Ser	Gln 95 Leu	80 Trp	
45	65 Cys Asp	Ser Thr	Glu Thr	Ile Gly 100	Trp 85 Leu	70 Gly Tyr	Asn Leu Ser	Ser Phe	Thr Ser	Pro 90 Glu	75 Asn Gln	Thr Thr	Ile Arg	Asp Ser	Gln 95 Leu	80 Trp Asp	
45	65 Cys Asp	Ser Thr	Glu Thr Leu	Ile Gly 100 Gln	Trp 85 Leu	70 Gly Tyr	Asn Leu Ser	Ser Phe Arg	Thr Ser 105 Lys	Pro 90 Glu	75 Asn Gln	Thr Thr	Ile Arg	Asp Ser	Gln 95 Leu	80 Trp Asp	
45	65 Cys Asp Gly	Ser Thr Arg	Glu Thr Leu 115	Ile Gly 100 Gln	Trp 85 Leu Val	70 Gly Tyr Ser	Asn Leu Ser His	Ser Phe Arg 120	Thr Ser 105 Lys	Pro 90 Glu Gly	75 Asn Gln Leu	Thr Thr Thr Pro	Ile Arg His 125	Asp Ser 110 Val	Gln 95 Leu Ile	80 Trp Asp Tyr	·
45	65 Cys Asp Gly	Ser Thr Arg	Glu Thr Leu 115 Leu	Ile Gly 100 Gln	Trp 85 Leu Val	70 Gly Tyr Ser	Asn Leu Ser His	Ser Phe Arg 120 Asp	Thr Ser 105 Lys	Pro 90 Glu Gly	75 Asn Gln Leu	Thr Thr Thr Pro	Ile Arg His 125	Asp Ser 110 Val	Gln 95 Leu	80 Trp Asp Tyr	
	65 Cys Asp Gly Cys	Ser Thr Arg Arg	Glu Thr Leu 115 Leu	Ile Gly 100 Gln Trp	Trp 85 Leu Val	70 Gly Tyr Ser Trp	Asn Leu Ser His Pro	Ser Phe Arg 120 Asp	Thr Ser 105 Lys Leu	Pro 90 Glu Gly His	75 Asn Gln Leu Ser	Thr Thr Thr Pro His 140	Ile Arg His 125 His	Asp Ser 110 Val Glu	Gln 95 Leu Ile Leu	80 Trp Asp Tyr Lys	
45	65 Cys Asp Gly Cys	Ser Thr Arg Arg	Glu Thr Leu 115 Leu	Ile Gly 100 Gln Trp	Trp 85 Leu Val	70 Gly Tyr Ser Trp	Asn Leu Ser His Pro 135 Tyr	Ser Phe Arg 120 Asp	Thr Ser 105 Lys Leu	Pro 90 Glu Gly His	75 Asn Gln Leu Ser	Thr Thr Thr Pro His 140	Ile Arg His 125 His	Asp Ser 110 Val Glu	Gln 95 Leu Ile	80 Trp Asp Tyr Lys	
	65 Cys Asp Gly Cys Ala 145	Ser Thr Arg Arg 130	Glu Thr Leu 115 Leu Glu	Ile Gly 100 Gln Trp Asn	Trp 85 Leu Val Arg Cys	70 Gly Tyr Ser Trp Glu 150	Asn Leu Ser His Pro 135 Tyr	Ser Phe Arg 120 Asp	Thr Ser 105 Lys Leu Phe	Pro 90 Glu Gly His	75 Asn Gln Leu Ser Leu 155	Thr Thr Thr Pro His 140 Lys	Ile Arg His 125 His Lys	Asp Ser 110 Val Glu Asp	Gln 95 Leu Ile Leu	Asp Tyr Lys Val	
	65 Cys Asp Gly Cys Ala 145	Ser Thr Arg Arg 130	Glu Thr Leu 115 Leu Glu	Ile Gly 100 Gln Trp Asn	Trp 85 Leu Val Arg Cys	70 Gly Tyr Ser Trp Glu 150	Asn Leu Ser His Pro 135 Tyr	Ser Phe Arg 120 Asp	Thr Ser 105 Lys Leu Phe	Pro 90 Glu Gly His	75 Asn Gln Leu Ser Leu 155	Thr Thr Thr Pro His 140 Lys	Ile Arg His 125 His Lys	Asp Ser 110 Val Glu Asp	Gln 95 Leu Ile Leu	Asp Tyr Lys Val 160 Pro	
	65 Cys Asp Gly Cys Ala 145 Cys	Ser Thr Arg Arg 130 Ile Val	Glu Thr Leu 115 Leu Glu Asn	Ile Gly 100 Gln Trp Asn Pro	Trp 85 Leu Val Arg Cys Tyr 165	70 Gly Tyr Ser Trp Glu 150 His	Asn Leu Ser His Pro 135 Tyr	Ser Phe Arg 120 Asp Ala Gln	Thr Ser 105 Lys Leu Phe Arg	Pro 90 Glu Gly His Asn Val	75 Asn Gln Leu Ser Leu 155 Glu	Thr Thr Pro His 140 Lys	Ile Arg His 125 His Lys Pro	Asp Ser 110 Val Glu Asp	Gln 95 Leu Ile Leu Glu Leu 175	Asp Tyr Lys Val 160 Pro	
	65 Cys Asp Gly Cys Ala 145 Cys	Ser Thr Arg Arg 130 Ile Val	Glu Thr Leu 115 Leu Glu Asn	Ile Gly 100 Gln Trp Asn Pro	Trp 85 Leu Val Arg Cys Tyr 165	70 Gly Tyr Ser Trp Glu 150 His	Asn Leu Ser His Pro 135 Tyr	Ser Phe Arg 120 Asp Ala Gln	Thr Ser 105 Lys Leu Phe Arg	Pro 90 Glu Gly His Asn Val	75 Asn Gln Leu Ser Leu 155 Glu	Thr Thr Pro His 140 Lys	Ile Arg His 125 His Lys Pro	Asp Ser 110 Val Glu Asp	Gln 95 Leu Ile Leu Glu Leu 175 Pro	Asp Tyr Lys Val 160 Pro	

			195					200					205			
	_	210	0				215	_				220	Pro			
5	Tyr 225	Ile	Ser	Glu	qaA	Gly 230	Glu	Thr	Ser	Asp	Gln 235	Gln	Leu	Asn	Gln	Ser 240
	Met	Asp	Thr	Gly	Ser 245	Pro	Ala	Glu	Leu	Ser 250	Pro	Thr	Thr	Leu	Ser 255	Pro
				260		-			265			_	Ser	270		
10	Phe	Trp	Cys 275	Ser	Ile	Ala	Tyr	Tyr 280	Glu	Leu	Asn	Gln	Arg 285	Val	Gly	Glu
		290					295					300	Gly			
15	305					310	•	-		_	315		Ser			320
	_				325					330			Gly		335	
				340					345				Cys	350		
20			355					360		_			Arg 365	_	-	
		370					375				_	380	Asn			
25	385					390					395		Ser			400
	_				405					410		_	Thr		415	
00				420					425			_	Gln	430		
30			435	_	_			440		•		_	Pro 445			
		450					455		_			460	Val			
35	ser 465	Met	ser.	Trp	vaı	470	Arg	Ala	Arg	Asp	475	Pro	Val	Ala	inr	480
		Ser	Lys	Gly	Glu 485		Leu	Phe	Thr	Gly 490		Val	Pro	Ile	Leu 495	
	Glu	Leu	qaA				Asn	_		_	Phe		Val	Ser 510		Glu
40	Gly	Glu	Gly 515	Asp	Ala	Thr	Tyr	Gly 520	Lys	Leu	Thr	Leu	Lys 525		Ile	Сув
	Thr	Thr 530	Gly	Lys	Leu	Pro	Val 535	Pro	Trp	Pro	Thr	Leu 540	Val	Thr	Thr	Let
45	545					550					555		His			560
					565					570			Val		575	
	Thr	Ile	Phe	Phe 580	Lys	Asp	Asp	Gly	Asn 585	Tyr	Lys	Thr	Arg	Ala 590	Glu	Va]
50	_		595		_			600					Leu 605			
	_	610					615			_		620				
55	625					630					635		Gln			640
	Tle	TAVE	Va 1	Asn	Phe	Tave	T la	Ara	Wic	y c n	Tla	Glu	Acn	GIV	Ser	Va]

										172								
					645					650					655			
	Gln	Leu	Ala	Asp 660	His	Tyr	Gln	Gln	Asn 665	Thr	Pro	Ile	Gly	Asp 670	Gly	Pro		
5	Val	Leu	Leu 675	Pro	Asp	Asn	His	Tyr 680	Leu	Ser	Thr	Gln	Ser 685	Ala	Leu	Ser		
	Lys	Asp 690		Asn	Glu	Lys	Arg 695	Asp	His	Met	Val	Leu 700	Leu	Glu	Phe	Val		
	Thr 705			Gly	Ile	Thr 710	Leu	Gly	Met	Asp	Glu 715	Leu	Tyr	Lys				
10			(2)	INE	FORM	TIOI	1 FOI	R SE() ID	NO:	76:					•		
		(:		EQUE														
15			(B) (C)	TYPE STRA	E: nu ANDEI	ones	ic ad	ingle										
			ii) N	MOLE	CULE				•			•					·	
20		(:		FEAT									,					
		·	(B)	NAM LOC	CATIO	ON: 3	1	2394	eque	nce								
25		()		OTI					: SE	Q ID	NO:	76:				• •		
														GAT			48	
30	1	АБР	ASII	Mec	5	116	IIII	ASII	1111	10	IIII	ser	ABII	Asp	15	Cys		
														GGA Gly			96	
35	200	-		20					25		• 5		U -1	30				
														AAG Lys			144	
			35		-	_							45	_		_	•	
40														ACT Thr			192	
		50					55					60						
45														TTG Leu		_	240	
	65					70					75					80		
														ATC Ile		_	288	
50					85					90					95			
														AAA Lys	_		336	
55				100					105					110				
	AAA	TAT	TGT	CAG	TAT	GCG	TTT	GAC	TTA	AAA	TGT	GAT	AGT	GTC	TGT	GTG	384	172

																	•	
	Lys	Tyr	Cys 115	Gln	Tyr	Ala	Phe	Asp 120	Leu	Lys	Cys	Asp	Ser 125	Val	Cys	Val ·	•	
5	AAT Asn	CCA Pro 130	TAT Tyr	CAC His	TAC Tyr	GAA Glu	CGA Arg 135	GTT Val	GTA Val	TCA Ser	CCT Pro	GGA Gly 140	ATT Ile	GAT Asp	CTC Leu	TCA Ser	432	
10										Ser			ATG Met				480	
													TCC Ser				528	
15	CAT His	TCA Ser	ATT Ile	CAA Gln 180	ACC Thr	ATC Ile	CAG Gln	CAT His	CCA Pro 185	CCA Pro	AGT Ser	AAT Asn	CGT Arg	GCA Ala 190	TCG Ser	ACA Thr	576	
20	GAG Glu	ACA Thr	TAC Tyr 195	AGC Ser	ACC	CCA Pro	GCT Ala	CTG Leu 200	TTA Leu	GCC Ala	CCA Pro	TCT Ser	GAG Glu 205	TCT	AAT Asn	GCT Ala	624	
25			Thr										TCC Ser				672	
30	CCT Pro 225	GCC Ala	AGT Ser	ATA Ile	CTG Leu	GGG Gly 230	Gly	AGC Ser	CAT	AGT Ser	GAA Glu 235	GGA Gly	CTG Leu	TTG Leu	CAG Gln	ATA Ile 240	720	
25	GCA Ala	TCA Ser	GGG Gly	CCT Pro	CAG Gln 245	Pro	GGA Gly	CAG Gln	CAG Gln	CAG Gln 250	Asn	GGA Gly	TTT Phe	ACT	GGT Gly 255	CAG Gln	768	•
35	CCA Pro	GCT Ala	ACT Thr	TAC Tyr 260	His	CAT	AAC Asn	AGC Ser	ACT Thr 265	Thr	ACC Thr	TGG	ACT Thr	GGA Gly 270	Ser	AGG Arg	816	
40				Tyr					Pro				AAC Asn 285	Gly		CTT	864	
45	CAG Gln	CAC His	His	CCG	CCI Pro	ATC Met	295	Pro	CAT His	CCC Pro	GGA Gly	CAT His	Tyr	TGG	CCI Pro	GTT Val	912	
50	CAC His	Asr	GAG Glu	CTI Leu	GCA Ala	TTC Phe 310	e Glr	CCT Pro	CCC Pro	ATI Ile	TCC Ser 315	Ası	CAT His	CCT Pro	GCT Ala	CCT Pro 320	960	
	GAG Glu	TAI	TGC Tr	TGI Cys	TC0 Se1	rIle	r GCT e Ala	г ТА(а Ту	r Phe	GAA Glu 330	ı Met	GA'	r GTT p Val	CAC L Glr	GT2 1 Va: 33	A GGA L Gly	1008	
55	GAC	ACI	A TT	OAA 1	GT.	r cc	r TC	A AG	C ·TG	c cc	r at:	r GT	r ac	r GT	r GA'	r GGA	1056	173

	Glu	Thr	Phe	Lys 340	Val	Pro	Ser	Ser	Cys 345	Pro	Ile	Val	Thr	Val 350	Asp	Gly	
5 .														CAA Gln			1104
10														CAC His			1152
15														TGG Trp			1200
														TTA Leu			1248
20														TAC Tyr 430			1296
25														CAG Gln		_	1344
30														GCA Ala			1392
35														ATA Ile			1440
														GAC Asp			1488
40														GGA Gly 510			1536
45														GAA Glu			1584
50														ACC Thr			1632
55														GCC Ala			1680
	GTG	AGC	AAG	GGC	GAG	GAG	CTG	TTC	ACC	GGG	GTG	GTG	CCC	ATC	CTG	GTC	1728

	Val	Ser	Lys	Gly		Glu	Leu	Phe	Thr	Gly	Val	Val	Pro	Ile	Leu	Val	•
					565					570					575		
5				GGC Gly 580													1776
10				GAT Asp													1824
15				AAG Lys													1872
10				GTG Val													1920
20				TTC Phe													1968
25				TTC Phe 660													2016
30				GGC Gly					Asn								2064
35				GAG Glu													2112
33				CAC His													2160
40				AAC Asn													2208
45	_			GAC Asp 740													2256
50				CCC Pro													2304
EE				AAC Asn	_												2352
55	ACC	GCC	GCC	GGG	ATC	ACT	CTC	GGC	ATG	GẠC	GAG	CTG	TAC	AAG	TAA		2397 175

WO 98/45704 PCT/DK98/00145

176

Thr Ala Ala Gly Ile Thr Leu Gly Met Asp Glu Leu Tyr Lys 785 790 795

5 (2) INFORMATION FOR SEQ ID NO:77:

- (i) SEQUENCE CHARACTERISTICS:
 - (A) LENGTH: 798 amino acids
 - (B) TYPE: amino acid
 - (C) STRANDEDNESS: single
 - (D) TOPOLOGY: linear
 - (ii) MOLECULE TYPE: protein
 - (v) FRAGMENT TYPE: internal

15

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(xi) SEQUENCE DESCRIPTION: SEQ ID NO:77:

	Met 1	Asp	Asn	Met	Ser 5	Ile	Thr	Asn	Thr	Pro 10	Thr	Ser	Asn	Asp	Ala 15	Cys
20	Leu	Ser	Ile	Val	His	Ser	Leu	Met	Cys 25	His	Arg	Gln	Gly	Gly 30	Glu	Ser
	Glu	Thr	Phe 35	Ala	Lys	Arg	Ala	Ile 40	Glu	Ser	Leu	Val	Lys 45	Lys	Leu	Lys
25	Glu	Lys 50	Lys	Asp	Glu	Leu	Asp 55	Ser	Leu	Ile	Thr	Ala 60	Ile	Thr	Thr	Asn
	Gly 65	Ala	His	Pro	Ser	Lys 70	Cys	Val	Thr	Ile	Gln 75	Arg	Thr	Leu	Asp	Gly 80
	Arg	Leu	Gln	Val	Ala 85	Gly	Arg	Lys	Gly	Phe 90	Pro	His	Val	Ile	Tyr 95	Ala
30	Arg	Leu	Trp	Arg 100	Trp	Pro	Asp	Leu	His 105	Lys	Asn	Glu	Leu	Lys 110	His	Val
	Lys	Tyr	Cys 115	Gln	Tyr	Ala	Phe	Asp 120	Leu	Lys	Cys	Asp	Ser 125	Val	Cys	Val
35	Asn	Pro 130	Tyr	His	Tyr	Glu	Arg 135	Val	Val	Ser	Pro	Gly 140	Ile	Asp	Leu	Ser
	Gly 145	Leu	Thr	Leu	Gln	Ser 150	Asn	Ala	Pro	Ser	Ser 155	Met	Met	Val	Lys	Asp 160
	Glu	Tyr	Val	His	Asp 165	Phe	Glu	Gly	Gln	Pro 170	Ser	Leu	Ser	Thr	Glu 175	_
40	His	Ser	Ile	Gln 180	Thr	Ile	Gln	His	Pro 185	Pro	Ser	Asn	Arg	Ala 190	Ser	Thr
	Glu	Thr	Tyr 195	Ser	Thr	Pro	Ala	Leu 200	Leu	Ala	Pro	Ser	Glu 205	Ser	Asn	Ala
45	Thr	Ser 210	Thr	Ala	Asn	Phe	Pro 215	Asn	Ile	Pro	Val	Ala 220	Ser	Thr	Ser	Gln
	Pro 225	Ala	Ser	Ile	Leu	Gly 230	Gly	Ser	His	Ser	Glu 235	Gly	Leu	Leu	Gln	Ile 240
	Ala	Ser	Gly	Pro	Gln 245	Pro	Gly	Gln	Gln	Gln 250	Asn	Gly	Phe	Thr	Gly 255	Gln
50	Pro	Ala	Thr	Tyr 260	His	His	Asn	Ser	Thr 265	Thr	Thr	Trp	Thr	Gly 270	Ser	Arg
	Thr	Ala	Pro 275	Tyr	Thr	Pro	Asn	Leu 280	Pro	His	His	Gln	Asn 285	Gly	His	Leu
55	Gln	His 290	His	Pro	Pro	Met	Pro 295	Pro	His	Pro	Gly	His 300	Tyr	Trp	Pro	Val
	His	Asn	Glu	Leu	Ala	Phe	Gln	Pro	Pro	Ile	Ser	Asn	His	Pro	Ala	Pro

		305					310					315					320
		Glu	Tyr	Trp	Cys	Ser	Ile	Ala	Tyr	Phe	Glu	Met	Asp	Val	Gln	Val	Gly
					_	325			•		330		•			335	
		Glu	Thr	Phe	Lys	Val	Pro	Ser	Ser	Cvs	Pro	Ile	Val	Thr	Val		Glv
	5				340					345					350		
		Tvr	Val	Asp	Pro	Ser	Glv	Glv	Asp		Phe	Cvs	Len	Glv	Gln	Len	Ser
		- 1 -		355			1	1	360	5				365		 u	
		Asn	Val		Ara	Thr	Glu	בומ		Glu	Ara	Δla	Ara		His	Tla	Gly
			370		5		O.Lu	375	110	GIU	Arg	AIG	380	пец	III	116	GIY
4	10	Lare		Val	Gln	T.All	Gl v		T 7.40	C1.,	C1	Cl.		1707	Trp	1701	7 ~~
	10	385	GIY	Val	GIII	шец	390	Cys	nys	GIY	GIU		Asp	vai	пр	val	
			Ton	50×	λ a.s.	77: -		17 1	Dh.	**- *	01	395	m	m	.		400
		Cys	пеп	SEI	weħ	405		Val	Pne	vaı		Ser	Tyr	Tyr	Leu		Arg
		~1	27-	~1	7			~ 3	. .:_		410	***	•	- 1	_	415	
	15	GIU	Ald	GIY		Ala	PIO	GIA	Авр		vaı	HIS	гÀ2	TIE	Tyr	Pro	ser
	13	77.		71.	420	17-7	Dl		.	425	-1		'	_	430		
		ATA	Tyr		гув	vai	Pne	Asp		Arg	GIn	Cys	His		Gln	Met	GIn
		~ 1	~ 1	435		ml			440					445	_ •		
		Gin		Ala	Ala	unr	Ата	•	Ala	Ala	Ala	Ala		Gln	Ala	Ala	Ala
,	20		450	-1	_		_	455	_			_	460	_	_	_	
. 4	20		Ala	GIY	Asn	ÌІе		GIA	Pro	Gly	Ser		Gly	Gly	Ile	Ala	
		465		_	_		470	_				475					480
		Ala	He	Ser	Leu		Ala	Ala	Ala	Gly		Gly	Val	qaA	Asp		Arg
			_	_		485					490					495	
		Arg	Leu	Cys		Leu	Arg	Met	Ser		Val	Lys	Gly	Trp	Gly	Pro	qaA
4	25				500		_			505					510		
		Tyr	Pro		Gln	Ser	Ile	Lys	Glu	Thr	Pro	Cys	Trp	Ile	Glu	Ile	His
				515					520					525			
		Leu		Arg	Ala	Leu	Gln	Leu	Leu	Ąsp	Glu	Val	Leu	His	Thr	Met	Pro
	_		530					535					540				
3	30		Ala	Asp	Pro	Gln	Pro	Leu	Asp	Trp	Asp	Pro	Pro	Val	Ala	Thr	Met
		545					550					555					560
		Val	Ser	Lys	Gly	Glu	Glu	Leu	Phe	Thr	Gly	Val	Val	Pro	Ile	Leu	Val
						565					570					575	
		Glu	Leu	Asp	Gly	Asp	Val	Asn	Gly	His	Lys	Phe	Ser	Val	Ser	Gly	Glu
3	35				580					585					590		
		Gly	Glu	Gly	Asp	Ala	Thr	Tyr	Gly	Lys	Leu	Thr	Leu	Lys	Phe	Ile	Cys
				595					600					605			
		Thr	Thr	Gly	Lys	Leu	ЬĽО	Val	Pro	Trp	Pro	Thr	Leu	Val	Thr	Thr	Leu
			610					615					620				
4	10	Thr	Tyr	Gly	Val	Gln	Cys	Phe	Ser	Arg	Tyr	Pro	Asp	His	Met	Lys	Gln
		625					630					635					640
		His	Asp	Phe	Phe	Lys	Ser	Ala	Met	Pro	Glu	Gly	Tyr	Val	Gln	Glu	Arg
						645					650					655	
		Thr	Ile	Phe	Phe	Lys	Asp	Asp	Gly	Asn	Tyr	Lys	Thr	Arg	Ala	Glu	Val
4	15				660					665					670		
		Lys	Phe	Glu	Gly	Asp	Thr	Leu	Val	Asn	Arg	Ile	Glu	Leu	Lys	Gly	Ile
				675					680					685			
		Asp	Phe	Lys	Glu	Asp	Gly	Asn	Ile	Leu	Gly	His	Lys	Leu	Glu	Tyr	Asn
			690					695					700			-	•
5	50	Tyr	Asn	Ser	His	Asn	Val	Tyr	Ile	Met	Ala	Asp	Lys	Gln	Lys	Asn	Gly
		705					710	_				715	-		-		720
		Ile	Lys	Val	Asn	Phe		Ile	Arq	His	Asn		Glu	asa	Gly	Ser	
			-			725	-		_		730			-	4	735	
		Gln	Leu	Ala	Asp	His	Tyr	Gln	Gln	Asn		Pro	Ile	Gly	Asp		Pro
5	55				740		-			745				-	750	-	
٠		Val	Leu	Leu	Pro	Asp	Asn	His	Tyr		Ser	Thr	Gln	Ser	Ala	Leu	Ser
						-		-	<i>4</i> –								

										1/8			•					
			755					760					765					
	Lys	Asp 770	Pro	Asn	Glu	Lys	Arg 775	Asp	His	Met	Val	Leu 780	Leu	Glu	Phe	Val		
	Thr		Ala	Gly	Ile	Thr		Gly	Met	Asp	Glu		Tyr	Lys				
5	785			-		790		-		-	795		_	-		•		
			(2)	INE	ORMA	MOIT	rof	SEC) ID	NO:7	8:			. •				
		(:	i) SI	EQUEN	ICE C	HAR	CTEF	RISTI	CS:				•					
10				LENG				_	irs						٠	•		
				TYPE STRA					.									
			(D)	TOPO	LOG	: li	near	•										
15		. (:	ii) N	OLEC	CULE	TYPE	: cI	NA .										
				FEAT														
				IAN				-	equer	ice								
20			• • • •	LOC			-											
20			(-,										•					
		(2	(i) S	SEQUE	ENCE	DESC	RIPT	: NOI	SEC) ID	NO:	78:						
														GCG			48	•
25		Ala	Gly	Trp	Ile 5	Gln	Ala	Gln	Gln	Leu 10	Gln	Gly	Asp	Ala	Leu 15	Arg		
	1				.					10					13			
														GTC Val			96	
30	GIII	Mec	GIII	20	Tien	ıyı	Сту	GIII	25	PILE	PIU	110	Gru	30	nr 9	1170		
	mi a	mma	CO C	G2 G	maa.	n mm	030	200	an a	aan	maa	C A TT	ccc	א יייייי	CNC	TOTAL CO	144	
														ATT Ile			144	
25	_		35					40					45					
35	GAC	AAT	CCC	CAG	GAC	AGA	GCC	CAA	GCC	ACC	CAG	CTC	CTG	GAG	GGC	CTG	192	
	Asp		Pro	Gln	Asp	Arg							Leu	Glu	Gly	Leu		
		50					55					60						
40														GAA		_	240	
	Val 65	Gln	Glu	Leu	Gln	Lys 70	Lys	Ala	Glu	His	Gln 75	Val	Gly	Glu	Asp	80 GIÀ		
	03				,													
45														CTC Leu			288	
40	PHE	neu	пец	БУБ	85	шуз	neu	GIŢ	urs	90	ATO	1111	GIII	ДСИ	95	27.5	i	
		ma m	030		maa	CCC	C/TrO	C3.C	CTC.	~m~	000	mcc	א מייכי	CCC	CNC	אייניי	336	
														CGG Arg			330	
50	•	_		100					105					110				
	CTG	TAC	AAT	GAA	CAG	AGG	CTG	GTC	CGA	GAA	GCC	AAC	AAT	TGC	AGC	TCT	384	
			Asn					Val					Asn	Cys				
55			115					120					125					
	CCG	GCT	GGG	ATC	CTG	GTT	GAC	GCC	ATG	TCC	CAG	AAG	CAC	CTT	CAG	ATC	432	
																		178

	Pro	Ala 130	Gly	Ile	Leu	Val	Asp 135	Ala	Met	Ser	Gln	Lys 140	His	Leu	Gln	Ile	
5									CTG Leu								480
10									CAG Gln								528
15									CAG Gln 185								576
10									GAG Glu								624
20				•					CGT Arg								672
25									CAC His								720
30									GAT Asp								768
35									GGC Gly 265								816
55									AAG Lys							_	864
40									GAG Glu								912
45									CTG Leu								960
50				-				-	ACC. Thr								1008
55									CAG Gln 345							_	1056
J J	CGC	CTG	CTG	GTG	GGC	GGG	AAG	CTG	AAC	GŢG	CAC	ATG	AAT	CCC	CĆC	CAG	1104

										.00							
	Arg	Leu	Leu 355	Val	Gly	Gly	Lys	Leu 360		Val	His	Met	Asn 365	Pro	Pro	Gln	
	GTG	DAG	GCC	ACC	ΔTC	ΔTC	ΣСΤ	GAG	CAG	CAG	GCC	מממ	ጥርጥ	CTG	CTT	ΔΔΔ	1152
5															Leu		1172
J	Vai	370				110	375	oru	0111	UIII	ALU	380	DCL			.,.	
	AAT	GAG	AAC	ACC	CGC	AAC	GAG	TGC	AGT	GGT	GAG	ATC	CTG	AAC	AAC	TGC	1200
	Asn	Glu	Asn	Thr	Arg	Asn	Glu	Cys	Ser	Gly	Glu	Ile	Leu	Asn	Asn	Cys	
10	385					390					395					400	
															CAC		1248
	Cys	Val	Met	Glu	Tyr	His	Gln	Ala	Thr	Gly	Thr	Leu	Ser	Ala	His	Phe	
					405					410					415		
15																	
															GGT		1296
	Arg	Asn	Met		Leu	Lys	Arg	Ile	-	Arg	Ala	Asp	Arg		Gly	Ala	
				420					425					430	•		
20	CNC	maa	CTC	א כיא	CAC	מאפ	አአሮ	TT C	202	ama	CTC	നസൻ	CAC	Tr Carr	CAG	TTC	1344
20															Gln		1344
	Giu	Ser	435	1111	GIU	GIU	Lys	440	1111	VAI	Tien	FIIC	445	JCI	0111	FIIC	
			133					440					443				•
	AGT	GTT	GGC	AGC	AAT	GAG	CTT	GTG	TTC	CAG	GTG	AAG	ACT	CTG	TCC	CTA	1392
25															Ser		
		450	•				455					460					
	CCT	GTG	GTT	GTC	ATC	GTC	CAC	GGC	AGC	CAG	GAC	CAC	AAT	GCC	ACG	GCT	1440
	Pro	Val	Val	Val	Ile	Val	His	Gly	Ser	Gln	Asp	His	Asn	Ala	Thr	Ala	
30 .	465					470					475					480	
															CCA		1488
	Thr	Val	Leu	Trp		Asn	Ala	Phe	Ala		Pro	GIÀ	Arg	vaı	Pro	Pne	
25					485					490					495		
35	ccc	CTC	CCT	GNC	מממ	GTG	CTC	TCC	CCG	CNG	CTC	ጥርጥ	GAG	aca	CTC	מממ	1536
															Leu		1330
	YIG	Val	110	500	Lly 5	vai	DCu	TTP	505	GIII	пси	Cyb	OIU	510			
				500					505								
40	ATG	AAA	TTC	AAG	GCC	GAA	GTG	CAG	AGC	AAC	CGG	GGC	CTG	ACC	AAG	GAG	1584
	Met	Lys	Phe	Lys	Ala	Glu	Val	Gln	Ser	Asn	Arg	Gly	Leu	Thr	Lys	Glu	
			515					520					525				
	AAC	CTC	GTG	TTC	CTG	GCG	CAG	AAA	CTG	TTC	AAC	AAC	AGC	AGC	AGC	CAC	1632
45	Asn	Leu	Val	Phe	Leu	Ala	Gln	Lys	Leu	Phe	Asn	Asn	Ser	Ser	Ser	His	
•		530					535					540				•	
		a	a			~~~							~ • •	m		200	
												*			AAC		1680
EO		GIU	Asp	ıyr	ser		ьеи	ser	Val	ser	-		GIN	ьие	Asn		
50	545					550					555					560	
	CDC	አአጣ	تاملمك	CCC	GGC	ጥርር	ם א מ	ጥ አ ጣ	אכם	ጥጥጣ	TOO	ראכ	TOO	بلىنلىنل	GAC	GGG	1728
					_									_	Asp		1/20
	GIU	Lon	Leu		565	11p	wan	T Y L	# 11#	570	rrb	G111	11p		575	- - 3	
55					505					5,0		•			٠, ٥		
	GTG	ATG	GAG	GTG	TTG	AAG	AAG	CAC	CAC	AAG	CCC	CAC	TGG	AAT	GAT	GGG	1776

		Val	Met	Glu	Val 580	Leu	Lys	Lys	His	His 585	Lys	Pro	His	Trp	Asn 590	Asp	Gly	•
		GCC	אידכ	СТЛ	CCT	TTT	CTC	ידממ	מממ	ראא	CAG	GCC	כאכ	GAC	כיזיכי	CTC	አጥ ር	1824
	5 .					Phe												1024
		ממ	AAG	CCC	GAC	GGG	ACC	ттс	חידים	ጥጥር	ccc	ጥጥጥ	ъcт	GAC	тса	CDD	አጥ <u>ሮ</u>	1872
						Gly												1072
	10	ASII	610	110	пор	Oly	****	615	Deu	Deu			620	Авр	DCL	OIU	7	
		GGG	GGC	ATC	ACC	ATC	GCC	TGG	AAG	TTT	GAC	TCC	CCG	GAA	CGC	AAC	CTG	1920
		Gly	Gly	Ile	Thr	Ile	Ala	Trp	Lys	Phe	Asp	Ser	Pro	Glu	Arg	Asn	Leu	
		625					63,0		-		_	635					640	
	15																	
		TGG	AAC	CTG	AAA	CCA	TTC	ACC	ACG	CGG	GAT	TTC	TCC	ATC	AGG	TCC	CTG	1968
		Trp	Asn	Leu	Lys	Pro	Phe	Thr	Thr	Arg	Asp	Phe	Ser	Ile	Arg	Ser	Leu	
						645					650			•		655		
	20	ССТ	GAC	CGG	CTG	GGG	GAC	CTG	AGC	יי מיי	CTC	ATC	тат	GTG	արգո	ССТ	GAC	2016
•	20					Gly												2010
			11.55	••• 5	660	0-1				665	Deu		-1-		670			
										000					0,0			
		CGC	CCC	AAG	GAT	GAG	GTC	TTC	TCC	AAG	TAC	TAC	ACT	ССТ	GTG	CTG	GCT	2064
	25					Glu												
				675	•				680	•	•	- 4		685				
															•			
		AAA	GCT	GTT	GAT	GGA	TAT	GTG	AAA	CCA	CAG	ATC	AAG	CAA	GTG	GTC	CCT	2112
		Lys	Ala	Val	Asp	Gly	Tyr	Val	Lys	Pro	Gln	Ile	Lys	Gln	Val	Val	Pro	
	30		690					695					700					
						GCA									•			2160
			Phe	Val	Asn	Ala		Ala	Asp	Ala	Gly	-	Ser	Ser	Ala	Thr		
	٥٣	705					710					715					720	
	35	> ===	a	a. a	~~~		maa	GG3	aam	-		~~~	~~~	0.0m	-	CD 2 CD	220	2200
						CCC												2208
		met	Asp	Gin	Ата	Pro	ser	Pro	Ата	vai	-	Pro	Gin	AIA	Pro		ASII	
						725					730					735		
	40	ATG	TAC	CCA	CAG	AAC	CCT	GAC	САТ	GTA	СТС	GAT	CAG	САТ	GGA	GAA	TTC	2256
						Asn												
			-1-		740			F		745					750			
		GAC	CTG	GAT	GAG	ACC	ATG	GAT	GTG	GCC	AGG	CAC	GTG	GAG	GAA	CTC	TTA	2304
	45	Asp	Leu	Asp	Glu	Thr	Met	Asp	Val	Ala	Arq	His	Val	Glu	Glu	Leu	Leu	
		-		755				-	760		_			765				
		CGC	CGA	CCA	ATG	GAC	AGT	CTT	GAC	TCC	CGC	CTC	TCG	CCC	CCT	GCC	GGT	2352
		Arg	Arg	Pro	Met	Asp	Ser	Leu	Asp	Ser	Arg	Leu	Ser	Pro	Pro	Ala	Gly	
	50	_	770			_		775	_		_		780					
						GCC												2400
		Leu	Phe	Thr	Ser	Ala		Gly	Ser	Leu	Ser	Trp	Val	Pro	Arg	Ala		
		785					790					795					800	
	55												 -					
		GAT	CCA	CCG	GTC	GCC	ACC	ATG	GTG	AGC	AAG	GGC	GAG	GAG	CTG	TTC	ACC	2448

	qaA	Pro	Pro	Val	Ala 805	Thr	Met	Val	Ser	Lys 810	Gly	Glu	Glu	Leu	Phe 815	Thr	
	GGG	GTG	GTG	CCC	ATC	CTG	GTC	GAG	CTG	GAC	GGC	GAC	GTA	AAC	GGC	CAC	2496
5															Gly		
	AAG	TTC	AGC	GTG	TCC	GGC	GAG	GGC	GAG	GGC	GAT	GCC	ACC	TAC	GGC	AAG	2544
															Gly		
10			835	• .				840					845				
															CCC		2592
	Leu		ьеи	гля	Phe	IIe	_	Thr	Thr	Gly	Lys		Pro	Val	Pro	Trp	
15		850					855					860					
15	כככ	ACC	CTC	GTG	ACC	ACC	СТС	ACC	тас	GGC	GTG	CAG	TGC	תתכ י	AGC	CGC	2640
															Ser		2040
	865					870			-1-	1	875		-7-			880	•
								.*							•		
20	TAC	CCC	GAC	CAC	ATG	AAG	CAG	CAC	GAC	TTC	TTC	AAG	TCC	GCC	ATG	CCC	2688
	Tyr	Pro	Asp	His	Met	Lys	Gln	His	Asp	Phe	Phe	Lys	Ser	Ala	Met	Pro	
		•			885					890					895		
	(13.3	000	ma a	ama	a a	a . a	000		3 ma	mmc	mma		07.0	G3.G	000		0506
25															GGC Gly		2736
20	GIU	Gry	LYL	900	0111	GIU	ALG	1111	905	FIIC	FIIC	Буб	veb	910	Giy	ABII	
	TAC	AAG	ACC	CGC	GCC	GAG	GTG	AAG	TTC	GAG	GGC	GAC	ACC	CTG	GTG	AAC	2784
	Tyr	Lys	Thr	Arg	Ala	Glu	Val	Lys	Phe	Glu	Gly	Asp	Thr	Leu	Val	Asn	
30			915					920					925				
	áaa	N III CI	C2C	ama	220	000	» ma	an a	mma	220	ar a	an a	000	n n a	a ma	C/MCI	2022
															ATC Ile		2832
	9	930			٠, ٥	CLY	935	иор	1110	·	014	940	017	71011		200	
35		•															
	GGG	CAC	AAG	CTG	GAG	TAC	AAC	TAC	AAC	AGC	CAC	AAC	GTC	TAT	ATC	ATG	2880
	Gly	His	Lys	Leu	Glu	Tyr	Asn	Tyr	Asn	Ser	His	Asn	Val	Tyr	Ile	Met	
	945					950					955					960	
40	ecc	GNO	አአጥ	ראת	חתת	ח ת ת	GGG	አጥጣ	አአጣ	GTC	א א מ	արու	አአጣ	איזירי	CGC	CAC	2928
40															Arg		2926
					965		U #1	110	2,5	970			_, _		975		
	AAC	ATC	GAG	GAC	GGC	AGC	GTG	CAG	CTC	GCC	GAC	CAC	TAC	CAG	CAG	.AAC	2976
45	Asn	Ile	Glu	Asp	Gly	Ser	Val	Gln	Leu	Ala	Asp	His	Tyr	Gln	Gln	Asn	
				980					985					990			
·				~~~	~~ ~									~~ ~		ama	
															TAC		3024
50	Inr	Pro	995	GIY	Asp	GIY		vaı 1000	Leu	Leu	Pro	_	ASN 1005	HIS	Tyr	neu	
			טעע														
	AGC	ACC	CAG	TCC	GCC	CTG	AGC	ÀAA	GAC	CCC	AAC	GAG	AAG	CGC	GAT	CAC	3072
															Asp		
		1010					1015	-	_			1020	-				
55	_														_		_
	ATG	GTC	CTG	CTG	GAG	TTC	GTG	ACC	GCC	GCC	GGG	ATC	ACT	CTC	GGC	ATG	3120

183 Met Val Leu Leu Glu Phe Val Thr Ala Ala Gly Ile Thr Leu Gly Met 1025 1030 1035 GAC GAG CTG TAC AAG TAA 3138 5 Asp Glu Leu Tyr Lys 1045 (2) INFORMATION FOR SEQ ID NO:79: 10 (i) SEQUENCE CHARACTERISTICS: (A) LENGTH: 1045 amino acids (B) TYPE: amino acid (C) STRANDEDNESS: single (D) TOPOLOGY: linear 15 (ii) MOLECULE TYPE: protein (v) FRAGMENT TYPE: internal 20 (xi) SEQUENCE DESCRIPTION: SEQ ID NO:79:

Met Ala Gly Trp Ile Gln Ala Gln Gln Leu Gln Gly Asp Ala Leu Arg Gln Met Gln Val Leu Tyr Gly Gln His Phe Pro Ile Glu Val Arg His 25 Tyr Leu Ala Gln Trp Ile Glu Ser Gln Pro Trp Asp Ala Ile Asp Leu Asp Asn Pro Gln Asp Arg Ala Gln Ala Thr Gln Leu Leu Glu Gly Leu 30 Val Gln Glu Leu Gln Lys Lys Ala Glu His Gln Val Gly Glu Asp Gly 70 75 Phe Leu Leu Lys Ile Lys Leu Gly His Tyr Ala Thr Gln Leu Gln Lys 90 Thr Tyr Asp Arg Cys Pro Leu Glu Leu Val Arg Cys Ile Arg His Ile 35 100 105 Leu Tyr Asn Glu Gln Arg Leu Val Arg Glu Ala Asn Asn Cys Ser Ser 120 Pro Ala Gly Ile Leu Val Asp Ala Met Ser Gln Lys His Leu Gln Ile 135 40 Asn Gln Thr Phe Glu Glu Leu Arg Leu Val Thr Gln Asp Thr Glu Asn 155 150 Glu Leu Lys Lys Leu Gln Gln Thr Gln Glu Tyr Phe Ile Ile Gln Tyr 170 Gln Glu Ser Leu Arg Ile Gln Ala Gln Phe Ala Gln Leu Ala Gln Leu 45 185 Ser Pro Gln Glu Arg Leu Ser Arg Glu Thr Ala Leu Gln Gln Lys Gln 200 Val Ser Leu Glu Ala Trp Leu Gln Arg Glu Ala Gln Thr Leu Gln Gln 215 220 Tyr Arg Val Glu Leu Ala Glu Lys His Gln Lys Thr Leu Gln Leu Leu 50 230 235 Arg Lys Gln Gln Thr Ile Ile Leu Asp Asp Glu Leu Ile Gln Trp Lys 250 Arg Arg Gln Gln Leu Ala Gly Asn Gly Gly Pro Pro Glu Gly Ser Leu 55 265 Asp Val Leu Gln Ser Trp Cys Glu Lys Leu Ala Glu Ile Ile Trp Gln

			275					280					285			
	Asn	Arg 290	Gln	Gln	Ile	Arg	Arg 295	Ala	Glu	His	Leu	ay2	Gln	Gln	Leu	Pro
5	Ile 305	Pro	Gly	Pro	Val	Glu 310	Glu	Met	Leu	Ala	Glu 315	Val	Asn	Ala	Thr	Ile 320
	Thr	Asp	Ile	Ile	Ser 325	Ala	Leu	Val	Thr	Ser 330	Thr	Phe	Ile	Ile	Glu 335	Lys
	Gln	Pro	Pro	Gln 340	Val	Leu	Lys	Thr	Gln 345	Thr	Lys	Phe	Ala	Ala 350	Thr	Val
10	Arg	Leu	Leu 355	Val	Gly	Gly	Lys	Leu 360	Asn	Val	His	Met	Asn 365	Pro	Pro	Gln
•		Lys 370					375					380				
15	385	Glu				390				•	395					400
	_	Val			405					410					415	
	_	Asn		420					425	_		· -		430	_	
20		Ser	435				_	440					445			
		450					455					460				Leu
25	465					470					475					Ala 480
		Val			485					490					495	
00		Val		500				-	505					510		
30		Lys	515					520				_	525			
		Leu 530					535	_				540				
35	545	Glu	_			550					555					560
					565			-		570	_		_		575	Gly
40				580					585	-			_	590	_	
40	:		595	_				600					605			Ile
		610					615					620			٠.	Ile
45	625					630		_		_	635					Leu 640
	_				645				_	650					655	Leu
50				660					665			-		670		Asp
50	_		675					680	-		_		685			Ala
	_	690					695					700				Pro
55	705					710					715					Tyr 720 Asn
	1-15	Toh		TTO			FIG	vid	val	∟y S	PIO	GIII	urq	PIQ	TAT	woll

					725					730					735				
	Met	Tyr	Pro	Gln 740	Asn	Pro	Asp	His	Val 745	Leu	qaA	Gln	Asp	Gly 750	Glu	Phe			
5	Asp	Leu	Asp 755	Glu	Thr	Met	Asp	Val 760	Ala	Arg	His	Val	Glu 765	Glu	Leu	Leu			
•	Arg	Arg 770	Pro	Met	Asp	Ser	Leu 775	Asp	Ser	Arg	Ļeu	Ser 780	Pro	Pro	Ala	Gly			
	Leu 785	Phe	Thr	Ser	Ala	Arg 790	Gly	Ser	Leu	Ser	Trp 795	Val	Pro	Arg	Ala	Arg 800			
10		Pro	Pro	Val	Ala 805	Thr	Met	Val	Ser	Lys 810	Gly	Glu	Glu	Leu	Phe 815	Thr			
	Gly	Val	Val	Pro 820	Ile	Leu	Val	Glu	Leu 825	Asp	Gly	Asp	Val	Asn 830	Gly	His			
15	Lys	Phe	Ser 835	Val	Ser	Gly	Glu	Gly 840	Glu	Gly	Asp	Ala	Thr 845	Tyr	Gly	Lys			
	Leu	Thr 850	Leu	Lys	Phe	Ile	Cys 855	Thr	Thr	Gly	Lys	Leu 860	Pro	Val	Pro	Trp			
	Pro 865	Thr	Leu	Val	Thr	Thr 870	Leu	Thr	Tyr	Gly	Val 875	Gln	Cys	Phe	Ser	Arg 880			
20	-	Pro			885	_				890					895				
		Gly		900					905					910					
25	-	Lys	915	_		,		920			_	_	925						
	_	Ile 930					935					940							
	945	His				950	•				955					960			
30		Asp	_		965					970					975				
		Ile		980					985					990					
35		Pro	995					1000					1005						
		Thr 1010 Val					1015					1020							
40	025	Glu				1030	vaı	1111	AIG		1035		1111	Dea		1040			
70	veb	GIU	Бей	_	1045														
			(2) IN	FORM	OITA	N FO	R SE	Q ID	NO:	80:						,		
45		(EQUE LEN												V.			
			(B)	TYP STR	E: n	ucle	ic a	cid											
50			(D)	TOP	olog	Y: l	inea	r											
		(xi)	SEQU	ENCE	DES	CRIP	TION	: SE	Q II	NO:	80:							
•	TGG	GATC	CTC	AGGC	CGTG	CT G	CTGG	CCG										2	8
55			(2) IN	FORM	ATIO	N FC	R SE	Q II	NO:	81:								
																			185

5	(i) SEQUENCE CHARACTERISTICS:(A) LENGTH: 27 base pairs(B) TYPE: nucleic acid(C) STRANDEDNESS: single(D) TOPOLOGY: linear		
	(xi) SEQUENCE DESCRIPTION: SEQ ID NO:81:		
10	GTCTCGAGGG AGCATGGGCA CCTTGCG		27
	(2) INFORMATION FOR SEQ ID NO:82:		
15	(i) SEQUENCE CHARACTERISTICS: (A) LENGTH: 27 base pairs (B) TYPE: nucleic acid		
20	(C) STRANDEDNESS: single (D) TOPOLOGY: linear		
	(xi) SEQUENCE DESCRIPTION: SEQ ID NO:82:	•	
25	TGGGATCCGA GAAGTCTATA TCCCATC	·	27
25	(2) INFORMATION FOR SEQ ID NO:83:		
	(i) SEQUENCE CHARACTERISTICS:(A) LENGTH: 28 base pairs		
30	(B) TYPE: nucleic acid(C) STRANDEDNESS: single(D) TOPOLOGY: linear		
35	(xi) SEQUENCE DESCRIPTION: SEQ ID NO:83:		
	TGGGATCCTT AGAAGTCTAT ATCCCATC		28
40	(2) INFORMATION FOR SEQ ID NO:84:		
	(i) SEQUENCE CHARACTERISTICS:(A) LENGTH: 28 base pairs(B) TYPE: nucleic acid(C) STRANDEDNESS: single		
45	(D) TOPOLOGY: linear		
	(xi) SEQUENCE DESCRIPTION: SEQ ID NO:84:	,	
50	GTCTCGAGCC ATGAACGCCC CCGAGCGG		28
	(2) INFORMATION FOR SEQ ID NO:85:		٠.
55	(i) SEQUENCE CHARACTERISTICS:(A) LENGTH: 30 base pairs(B) TYPE: nucleic acid		
			186

	(C) STRANDEDNESS: single (D) TOPOLOGY: linear	·
5	(xi) SEQUENCE DESCRIPTION: SEQ ID NO:85:	
	GTGAATTCTC GTCTGATTTC TGGCAGGAGG	30
10	(2) INFORMATION FOR SEQ ID NO:86:	
	(i) SEQUENCE CHARACTERISTICS:(A) LENGTH: 30 base pairs(B) TYPE: nucleic acid(C) STRANDEDNESS: single	
15	(D) TOPOLOGY: linear	•
	(xi) SEQUENCE DESCRIPTION: SEQ ID NO:86:	
20	GTGAATTCTT TACGTCTGAT TTCTGGCAGG	30
	(2) INFORMATION FOR SEQ ID NO:87:	
25	(i) SEQUENCE CHARACTERISTICS:(A) LENGTH: 34 base pairs(B) TYPE: nucleic acid(C) STRANDEDNESS: single(D) TOPOLOGY: linear	
30	(-:)	
	(xi) SEQUENCE DESCRIPTION: SEQ ID NO:87:	34
35	GTCTCGAGCC ATGGACGAAC TGTTCCCCCT CATC (2) INFORMATION FOR SEQ ID NO:88:	31
33	(i) SEQUENCE CHARACTERISTICS:	
40	(A) LENGTH: 31 base pairs(B) TYPE: nucleic acid(C) STRANDEDNESS: single(D) TOPOLOGY: linear	
45	(xi) SEQUENCE DESCRIPTION: SEQ ID NO:88:	
	GTGGATCCAA GGAGCTGATC TGACTCAGCA G	31
	(2) INFORMATION FOR SEQ ID NO:89:	
50	 (i) SEQUENCE CHARACTERISTICS: (A) LENGTH: 32 base pairs (B) TYPE: nucleic acid (C) STRANDEDNESS: single (D) TOPOLOGY: linear 	
55	(D) TOPOLOGI. TIMERL	

	(xi) SEQUENCE DESCRIPTION: SEQ ID NO:89:	
	GTGGATCCTT AGGAGCTGAT CTGACTCAGC AG	32
5	(2) INFORMATION FOR SEQ ID NO:90:	
10	 (i) SEQUENCE CHARACTERISTICS: (A) LENGTH: 32 base pairs (B) TYPE: nucleic acid (C) STRANDEDNESS: single (D) TOPOLOGY: linear 	
15	(xi) SEQUENCE DESCRIPTION: SEQ ID NO:90:	
.5	CCTCCTAAGC TTATCATGGA CCATTATGAT TC	32
	(2) INFORMATION FOR SEQ ID NO:91:	
20	(i) SEQUENCE CHARACTERISTICS:(A) LENGTH: 33 base pairs(B) TYPE: nucleic acid(C) STRANDEDNESS: single	
25	(D) TOPOLOGY: linear (xi) SEQUENCE DESCRIPTION: SEQ ID NO:91:	
30	CCTCCTGGAT CCCTGCGCAG GATGATGGTC CAG (2) INFORMATION FOR SEQ ID NO:92:	33
35	(i) SEQUENCE CHARACTERISTICS: (A) LENGTH: 45 base pairs (B) TYPE: nucleic acid (C) STRANDEDNESS: single (D) TOPOLOGY: linear	
40	(xi) SEQUENCE DESCRIPTION: SEQ ID NO:92:	
	GGATGGAAGC TTCAATGGCT GCCATCCGGA AGAAACTGGT GATTG	45
45	(2) INFORMATION FOR SEQ ID NO:93:(i) SEQUENCE CHARACTERISTICS:(A) LENGTH: 45 base pairs	
50	(B) TYPE: nucleic acid (C) STRANDEDNESS: single (D) TOPOLOGY: linear	
	(xi) SEQUENCE DESCRIPTION: SEQ ID NO:93:	
55	GGATGGGGAT CCTCACAAGA CAAGGCAACC AGATTTTTTC TTCCC	45

	(2) INFORMATION FOR SEQ ID NO:94:		•
5	(i) SEQUENCE CHARACTERISTICS:(A) LENGTH: 29 base pairs(B) TYPE: nucleic acid(C) STRANDEDNESS: single		
	(D) TOPOLOGY: linear		
	• •		
10	(xi) SEQUENCE DESCRIPTION: SEQ ID NO:94:		
	GGGAAGCTTC CATGAGCGAG ACGGTCATC		29
45	(2) INFORMATION FOR SEQ ID NO:95:		
15	(i) SEQUENCE CHARACTERISTICS:(A) LENGTH: 28 base pairs(B) TYPE: nucleic acid		
20	(C) STRANDEDNESS: single (D) TOPOLOGY: linear		
	· ·		
	(xi) SEQUENCE DESCRIPTION: SEQ ID NO:95:		
25	CCCGGATCCT CAGGGAGAAC CCCGCTTC		28
	(2) INFORMATION FOR SEQ ID NO:96:		
30	(i) SEQUENCE CHARACTERISTICS:(A) LENGTH: 30 base pairs(B) TYPE: nucleic acid		
	(C) STRANDEDNESS: single (D) TOPOLOGY: linear	· .	
35	(xi) SEQUENCE DESCRIPTION: SEQ ID NO:96:		
	GTGAATTCGA CCATGGAGCG GCCCCCGGGG		30
40	(2) INFORMATION FOR SEQ ID NO:97:		
	(i) SEQUENCE CHARACTERISTICS: (A) LENGTH: 27 base pairs		
45	(B) TYPE: nucleic acid(C) STRANDEDNESS: single(D) TOPOLOGY: linear		
	(xi) SEQUENCE DESCRIPTION: SEQ ID NO:97:		
50	GTGGTACCCA TTCTGTTAAC CAACTCC		27
	(2) INFORMATION FOR SEQ ID NO:98:		
55	(i) SEQUENCE CHARACTERISTICS:		
	(A) LENGTH: 28 base pairs		189

	(B) TYPE: nucleic acid (C) STRANDEDNESS: single		
	(D) TOPOLOGY: linear		
5	(xi) SEQUENCE DESCRIPTION: SEQ ID NO:98:		
			28
	GTGGTACCTC ATTCTGTTAA CCAACTCC		20
10	(2) INFORMATION FOR SEQ ID NO:99:	•	
	(i) SEQUENCE CHARACTERISTICS:		
	(A) LENGTH: 28 base pairs(B) TYPE: nucleic acid	•	
15	(C) STRANDEDNESS: single		
13	(D) TOPOLOGY: linear		•
	(b) Toronodi. Tinear		
	(xi) SEQUENCE DESCRIPTION: SEQ ID NO:99:		
20			
	GTCTCGAGAG ATGCTGTCCC GTGGGTGG		28
	(2) INFORMATION FOR SEQ ID NO:100:		
25	(i) SEQUENCE CHARACTERISTICS:	• *	
	(A) LENGTH: 27 base pairs		
	(B) TYPE: nucleic acid		
	(C) STRANDEDNESS: single		
	(D) TOPOLOGY: linear		
30			
,	(xi) SEQUENCE DESCRIPTION: SEQ ID NO:100:		
	GTGAATTCGC TTCCTCTTGA GGGAACC		27
35	(2) INFORMATION FOR SEQ ID NO:101:		
	(2) INFORMATION FOR BLY IS NOTION.		
	(i) SEQUENCE CHARACTERISTICS:		
	(A) LENGTH: 27 base pairs		
40	(B) TYPE: nucleic acid	•	
	(C) STRANDEDNESS: single		
	(D) TOPOLOGY: linear		
45	(xi) SEQUENCE DESCRIPTION: SEQ ID NO:101:		
			27
	GTGAATTCAC TTCCTCTTGA GGGAACC		21
50	(2) INFORMATION FOR SEQ ID NO:102:		
-	(i) SEQUENCE CHARACTERISTICS:		
	(A) LENGTH: 29 base pairs		
	(B) TYPE: nucleic acid		
	(C) STRANDEDNESS: single		
55	(D) TOPOLOGY: linear		

	(xi) SEQUENCE DESCRIPTION: SEQ ID NO:102:	
_	GTCTCGAGCC ATGGAGAACT TCCAAAAGG	29
5	(2) INFORMATION FOR SEQ ID NO:103:	
	(i) SEQUENCE CHARACTERISTICS:	
10	(A) LENGTH: 28 base pairs (B) TYPE: nucleic acid	
10	(C) STRANDEDNESS: single	
	(D) TOPOLOGY: linear	•
15	(xi) SEQUENCE DESCRIPTION: SEQ ID NO:103:	
15		2.0
	GTGGATCCCA GAGTCGAAGA TGGGGTAC	28
20	(2) INFORMATION FOR SEQ ID NO:104:	
	(i) SEQUENCE CHARACTERISTICS:	
	(A) LENGTH: 29 base pairs (B) TYPE: nucleic acid	
	(C) STRANDEDNESS: single	
25	(D) TOPOLOGY: linear	
	(xi) SEQUENCE DESCRIPTION: SEQ ID NO:104:	
20	GTGGATCCTC AGAGTCGAAG ATGGGGTAC	29
30		25
	(2) INFORMATION FOR SEQ ID NO:105:	
	(i) SEQUENCE CHARACTERISTICS:	
35	(A) LENGTH: 30 base pairs (B) TYPE: nucleic acid	•
	(C) STRANDEDNESS: single	
	(D) TOPOLOGY: linear	
40		
	(xi) SEQUENCE DESCRIPTION: SEQ ID. NO:105:	
	GTGAATTCGG CGATGCCAGA CCCCGCGGCG	30
45	(2) INFORMATION FOR SEQ ID NO:106:	
	(i) SEQUENCE CHARACTERISTICS:	
	(A) LENGTH: 32 base pairs	
50	(B) TYPE: nucleic acid (C) STRANDEDNESS: single	
30	(D) TOPOLOGY: linear	
	, () analysis programme and the second of th	
55	(xi) SEQUENCE DESCRIPTION: SEQ ID NO:106:	
	GTGGATCCCA GGCACAGGCA GCCTCAGCCT TC	32
		191

			(2)	INF	ORMA	TION	FOR	SEQ	ID	NO:1	07:					•		
5		(i	(A) (B) (C)	LENG TYPE STRA	TH: : nu NDED	33 b clei NESS	CTER ease c ac : si near	pair id ngle	S									
10		, (x	ci) S	EQUE	NCE	DESC	RIPT	'ION :	SEC) ID	NO:1	07:						
	GTGG	ATC	CTC P	.GGCA	CAGG	C AG	CCTC	AGCC	TTC	:							33	
15			(2)	INF	ORMA	TION	FOR	SEC	ID	NO:1	08:							
20		(i	(A) (B) (C)	LENG TYPE STRA	TH: : nu NDEL	2616 clei NESS	CTER bas c ac s: si	e pa id ngle	irs									
25			(x) (A)	PEATU VAN	JRE: ME/KI	Y: C	e: cI	ıg Se	equer	nce								•
							L2 RMATI											
00									ana	. TD	NO 1	00.						
30		()	(1) 8	EQUE	SNCE	DESC	CRIPT	LON	: SEÇ	מד ז	NO: 1	.08:						
							GAG Glu										48	
35							GTA Val										96	Ĵ
40							ACC										144	
45							CCC Pro 55										192	
50							TGC Cys										240	
55							TCC Ser										288	
JŪ	CGC	ACC	ATC	TTC	TTC	AAG	GAC	GAC	GGC	AAC	TAC	AAG	ACC	CGC	GCC	GAG	336	192

	Arg	Thr	Ile	Phe 100	Phe	Lys	Asp	Asp	Gly 105	Asn	Tyr	Lys	Thr	Arg 110	Ala	Glu		•
5				GAG Glu												_		384
10		_		AAG Lys														432
45				AGC Ser										_				480
15				GTG Val											_			528
20				GCC Ala 180	_													576
25				CTG Leu											_			624
30				CCC Pro												TTC Phe		672
0.5				GCC Ala														720
35		_		TCT Ser														768
40				CTG Leu 260														816
45				CTG Leu													,	864
50				CTG Leu														912
												Gln				ACC Thr 320		960
55	TAC	GCC	ATT	GCC	GGC	GGC	AAA	GCG	CAC	TGT	GGA	CCG	GCA	GAG	CTC	TGC		1008

	Tyr	Ala	Ile	Ala	Gly 325	Gly	Lys	Ala	His	Cys 330	Gly	Pro	Ala	Glu	Leu 335	Сув	
5					CGC Arg												1056
10					CCG Pro												1104
15					GCC Ala											AAG Lys	1152
15					GCC Ala												1200
20					ATT Ile 405												1248
25					ACG Thr												1296
30					GGC Gly												1344
					TCC Ser												1392
35					AAG Lys												1440
40					TGG Trp 485												1488
45					TGC Cys								Ser				1536
50					GCT Ala				Thr								1584
					CAG Gln												1632
55	ACC	CCT	GAG	CCA	GCA	CGC	ATA	ACG	TCC	CCA	GAC	AAA	CCG	CGG	CCG	ATG	1680

										195							
	Thr 545	Pro	Glu	Pro	Ala	Arg 550	Ile	Thr	Ser	Pro	Asp 555	Lys	Pro	Arg	Pro	Met 560	
5					AGC Ser 565												1728
10					AAG Lys										_		1776
45					GGC Gly				•								1824
15					AAG Lys						Ala					AAG Lys	1872
20					AAG Lys												1920
25					CTG Leu 645												1968
30					GCC Ala												2016
35					TTC Phe												2064
33					CTG Leu	Leu		Gln			Met		Met				2112
40					TTT												2160
45					CAC His 725												2208
50					GAC Asp											AAG Lys	2256
																TTC Phe	2304
55	TCC	AGC	CGC	AGC	GAT	GTC	TGG	AGC	TAT	GGG	GTC	ACC	ATG	TGG	GAG	GCC	2352

	Ser	Ser 770	Arg	Ser	Asp		Trp 775	Ser	Tyr	Gly	Val	Thr 780	Met	Trp	Glu	Ala	
5		TCC Ser															2400
10		GCC Ala		Ile													2448
		CCC Pro														TGG Trp	2496
15		GAT Asp													_		2544
20		TAC Tyr 850															2592
25		GCT Ala						TGA									2616
30		(:	i) SI (A) (B)	EQUEI LENC TYPI	NCE (STH: E: ar	CHARI 871 mino	ACTEI amii acio	RIST: no a	ICS:	NO:	109:	•					
35		(:	(D)	STRA TOPO	DLOG:	Y: 1:	inea	r									
40		(1	v) FI	RAGMI	ENT :	TYPE	: in	tern	al	Q ID	NO:	109:					
	Met 1	Val	Ser	Lys	Gly 5	Glu	Glu	Leu	Phe	Thr	Gly	Val	Val	Pro	Ile 15	Leu	
45				20	_	_			25		_			30		Gly	
		_	35					40	_				45			Ile Thr	•
50	_	50			•		55					60				Lys	
	65 Gln	His	Asp	Phe		70 Lys	Ser	Ala	Met		75 Glu	Gly	Tyr	Val	Gln 95	80 Glu	
55	Arg	Thr	Ile	Phe		Lys	Asp	Asp	Gly		Tyr	Lys	Thr	Arg	Ala	Glu	٠ .
	Val	Lys	Phe			Asp	Thr	Leu			Arg	Ile	Glu	Leu	Lys	Gly	

			115					120					125			
	Ile	Asp		Lys	Glu	Asp	Gly 135	Asn	Ile	Leu	Gly	His 140	Lys	Leu	Glu	Tyr
	Acn			Ser	His	Asn		Tvr	Tle	Met	Δla		Lvs	Gln	Lvs	Asn
5	145	171	72012		****	150	***	-1-			155		_,_		-1-	160
3		Tle	Lvs	Val	Asn		Lvs	Tle	Ara	His		Ile	Glu	Asp	Glv	
	Cry				165		-1-		5	170				<u>F</u>	175	
٠.	Va 1	Gln	Leu	Ala	Asp	His	Tvr	Gln	Gln		Thr	Pro	Ile	Glv		
	• • • •	· · · ·		180	F		-1-		185			•		190		
10	Pro	Val	Leu	-	Pro	Asp	Asn	His		Leu	Ser	Thr	Gln	Ser	Ala	Leu
			195					200	- 7				205			
	Ser	Lvs		Pro	Asn	Glu	Lys	Arq	Asp	His	Met	Val	Leu	Leu	Glu	Phe
		210	•				215	_	•			220				
	Val	Thr	Ala	Ala	Gly	Ile	Thr	Leu	Gly	Met	Asp	Glu	Leu	Tyr	Lys	Ser
15	225				_	230					235					240
	Gly	Leu	Arg	Ser	Arg	Ala	Gln	Ala	Ser	Asn	Šer	Ala	Met	Pro	Asp	Pro
					245					250					255	
	Ala	Ala	His	Leu 260	Pro	Phe	Phe	Tyr	Gly 265	Ser	Ile	Ser	Arg	Ala 270	Glu	Ala
20	Glu	Glu	His		Lys	Leu	Ala	Glv	Met	Ala	Asp	Gly	Leu	Phe	Leu	Leu
	عبت		275		. – , –			280				2	285			
	Arg	Gln	Cys	Leu	Arg	Ser	Leu	Gly	Gly	Tyr	Val	Leu	Ser	Leu	Val	His
		290	•		_		295	•	_	-		300				
	Asp	Val	Arg	Phe	His	His	Phe	Pro	Ile	Glu	Arg	Gln	Leu	Asn	Gly	Thr
25	305					310					315					320
	Tyr	Ala	Ile	Ala	Gly	Gly	Lys	Ala	His	Cys	Gly	Pro	Ala	Glu	Leu	Cys
					325					330					335	_
	Glu	Phe	Tyr		Arg	Asp	Pro	Asp	_	Leu	Pro	Cys	Asn		Arg	Lys
			_	340	_	_		_	345	_	~-3	_	~ 3	350	n1	3
30	Pro	Cys		Arg	Pro	Ser	Gly		GIu	Pro	GIn	Pro		vaı	Pne	Asp
	_		355	3	7.7	14 a ta	17-1	360	N	(Th. exa	17.0 7	7. ~~	365	Thr	Trn	Lare
	Cys			Asp	Ala	Met	375	Arg	Asp	TYL	vaı	380	GIII	. 1111	ııp	цуъ
	7	370		C1. ,	Ala	Lou		Cln	717	Tla	Tla		-Gln	λla	Pro	Gln
35	385	GIU	GIY	GIU	ATO	390	GIU	GIII	ALG	116	395	JCI	0111	niu		400
33		Glu	Lva	T.e.11	Ile		Thr	Thr	Δla	His		Ara	Met	Pro	Trp	
	VAI	014	2,5	LCu	405		****			410		•••			415	- 4
	His	Ser	Ser	Leu	Thr		Glu	Glu	Ala		Arq	Lys	Leu	Tyr	Ser	Gly
				420		-,3			425		5			430		
40	Ala	Gln	Thr	Asp	Gly	Lys	Phe	Leu	Leu	Arg	Pro	Arg	Lys	Glu	Gln	Gly
			435	_	_			440					445			
	Thr	Tyr	Ala	Leu	Ser	Leu	Ile	Tyr	Gly	Lys	Thr	Val	Tyr	His	Tyr	Leu
		450					455					460				
	Ile	.Ser	Gln	Asp	Lys	Ala	Gly	Lys	Tyr	Cys	Ile	Pro	Glu	Gly	Thr	Lys
45	465					470					475					480
	Phe	Asp	Thr	Leu			Leu	Val	Glu			Lys	Leu	Lys		qaA
					485				_	490			_	_	495	
•	Gly	Leu	Ile			Leu	Lys	Glu			Pro	Asn	Ser			Ser
			_	500				_	505				***	510		Mb ~
50	Asn	Ala			Ala	Ата	Ala			Leu	Pro	Ala			Ser	Thr
	*	m\	515			7	7	520		mb	. T	7 ~~	525 Ser		Gl v	Tyr
	nea	530		PLO	G 111	ar 9	535		nsp	TIII	μen	540		rap	- Ly	~] _
	ጥኮ፦			Pro	בום.	Ara			Ser	Pro	Agn			Ara	Pro	Met
55	545		JIU	110	- ALG	550		****	SET	110	555			9		560
55			Asn	Thr	Ser			Glu	Ser	Pro			Asp	Pro	Glu	Glu
							- 4 -						1-			

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570
     Leu Lys Asp Lys Lys Leu Phe Leu Lys Arg Asp Asn Leu Leu Ile Ala
                                      585
     Asp Ile Glu Leu Gly Cys Gly Asn Phe Gly Ser Val Arg Gln Gly Val
5
     Tyr Arg Met Arg Lys Lys Gln Ile Asp Val Ala Ile Lys Val Leu Lys
                             615
     Gln Gly Thr Glu Lys Ala Asp Thr Glu Glu Met Met Arg Glu Ala Gln
                          630
                                              635
10
     Ile Met His Gln Leu Asp Asn Pro Tyr Ile Val Arg Leu Ile Gly Val
                      645
                                          650
     Cys Gln Ala Glu Ala Leu Met Leu Val Met Glu Met Ala Gly Gly Gly
                                      665
     Pro Leu His Lys Phe Leu Val Gly Lys Arg Glu Glu Ile Pro Val Ser
                                 680
15
      Asn Val Ala Glu Leu Leu His Gln Val Ser Met Gly Met Lys Tyr Leu
                              695
      Glu Glu Lys Asn Phe Val His Arg Asp Leu Ala Ala Arg Asn Val Leu
                          710
                                              715
      Leu Val Asn Arg His Tyr Ala Lys Ile Ser Asp Phe Gly Leu Ser Lys
20
                                          730
      Ala Leu Gly Ala Asp Asp Ser Tyr Tyr Thr Ala Arg Ser Ala Gly Lys
                                      745
      Trp Pro Leu Lys Trp Tyr Ala Pro Glu Cys Ile Asn Phe Arg Lys Phe
25
                                  760
      Ser Ser Arg Ser Asp Val Trp Ser Tyr Gly Val Thr Met Trp Glu Ala
                              775
      Leu Ser Tyr Gly Gln Lys Pro Tyr Lys Lys Met Lys Gly Pro Glu Val
                          790
                                              795
      Met Ala Phe Ile Glu Gln Gly Lys Arg Met Glu Cys Pro Pro Glu Cys
30
                      805
                                          810
      Pro Pro Glu Leu Tyr Ala Leu Met Ser Asp Cys Trp Ile Tyr Lys Trp
                                      825
      Glu Asp Arg Pro Asp Phe Leu Thr Val Glu Gln Arg Met Arg Ala Cys
35
                                  840
      Tyr Tyr Ser Leu Ala Ser Lys Val Glu Gly Pro Pro Gly Ser Thr Gln
      Lys Ala Glu Ala Ala Cys Ala
                          870
40
               (2) INFORMATION FOR SEQ ID NO:110:
            (i) SEQUENCE CHARACTERISTICS:
              (A) LENGTH: 2598 base pairs
45
              (B) TYPE: nucleic acid
              (C) STRANDEDNESS: single
              (D) TOPOLOGY: linear
            (ii) MOLECULE TYPE: cDNA
50
            (ix) FEATURE:
               (A) NAME/KEY: Coding Sequence
               (B) LOCATION: 1...2595
               (D) OTHER INFORMATION:
55
            (xi) SEQUENCE DESCRIPTION: SEQ ID NO:110:
```

	Met				Ala					Phe			GGC Gly					48
_	1				5					10					12			
5															~~~	000		0.5
													ATG					96
	Arg	Ala	Giu	A1a 20	Glu	GIu	His	Leu	Lуs 25	Leu	Ala	GIÀ	Met	30	Asp	GIÀ		
10	CTC.	ጥጥር	CTC	cma	CGC	CNG	TCC	CTG	CGC	TCG	СТС	GGC	GGC	тат	GTG	CTG		144
10													Gly					
	пец	FIIC	35	Deu	Arg.	GIM	СуБ	40		ĢCI.	Deu	01 ,	45	-1-	• • •			
	TCG	CTC	GTG	CAC	GAT	GTG	CGC	TTC	CAC	CAC	TTT	CCC	ATC	GAG	CGC	CAG		192
15													Ile					
		50					55				•	60						
	CTC	AAC	GGC	ACC	TAC	GCC	ATT	GCC	GGC	GGC	AAA	GCG	CAC	TGT	GGA	CCG		240
	Leu	Asn	Gly	Thr	Tyr	Ala	Ile	Ala	Gly	Gly	Lys	Ala	His	Cys	Gly	Pro.		
20	65					70					75					80		
													GGG					288
	Ala	Glu	Leu	Cys	Glu	Phe	Tyr	Ser	Arg	Asp	Pro	Asp	Gly	Leu	Pro	Cys		
					85					90					95			
25																		
													GAG					336
	Asn	Leu.	Arg		Pro	Cys	Asn	Arg		Ser	Gly	Leu	Glu	_	Gin	Pro		
				100					105					110				
••										>	ama	com	a	m 2 C	CTC	CCC		384
30													GAC					304
	GIA	vaı		Asp	Cys	Leu	Arg		Ala	Met	val	Arg	Asp	ıyı	val	Arg		
			115					120					125					•
	CNC	N.C.C.	TOO	אאכ	СТС	GNG	GGC	GNG	GCC	СТС	GAG	CAG	GCC	אידכי	ATC	AGC		432
35													Ala					
33	GIII	130	ııp	шуъ	Deu	Giu	135	Giu	AIA	Deu	GIU	140	niu			501		
		130					100											
	CAG	GCC	CCG	CAG	GTG	GAG	AAG	CTC	ATT	GCT	ACG	ACG	GCC	CAC	GAG	CGG		480
													Ala					
40	145					150	•				155					160		
							,											
	ATG	CCC	TGG	TAC	CAC	AGC	AGC	CTG	ACG	CGT	GAG	GAG	GCC	GAG	CGC	AAA		528
													Ala					
			_	_	165		•			170					175		٠	
45																		
	CTT	TAC	TCT	GGG	GCG	CAG	ACC	GAC	GGC	AAG	TTC	CTG	CTG	AGG	CCG	CGG		576
	Leu	Tyr	Ser	Gly	Ala	Gln	Thr	Asp	Gly	Lys	Phe	Leu	Leu	Arg	Pro	Arg		
				180					185					190		•		
50																GTG		624
	Lys	Glu	Gln	Gly	Thr	Tyr	Ala	Ĺeu	Ser	Leu	Ile	Tyr	Gly	Lys	Thr	Val		
			195					200					205					
																		_
•																CCC		672
55	Tyr		Tyr	Leu	Ile	Ser		_	Lys	Ala	Gly			Cys	Ile	Pro		
		210					215					220						

5		GGC Gly															720
		AAG Lys															768
10	Ser	AGT Ser	Ala	Ser 260	Asn	Ala	Ser	Gly	Ala 265	Ala	Ala	Pro	Thr	Leu 270	Pro	Ala .	816
15	His	CCA Pro	Ser 275	Thr	Leu	Thr	His	Pro 280	Gln	Arg	Arg	Ile	Asp 285	Thr	Leu	Asn	864
20	Ser	GAT Asp 290	Gly	Tyr	Thr	Pro	Glu 295	Pro	Ala	Arg	Ile	Thr 300	Ser	Pro	Asp	Lys	912
25	Pro 305	CGG Arg	Pro	Met	Pro	Met 310	Asp	Thr	Ser	Val	Tyr 315	Glu	Ser	Pro	Tyr	Ser 320	960
		CCA Pro															1008
30		CTC Leu															1056
35		CAG Gln															1104
40		GTG Val 370															1152
45		GAG Glu															1200
		ATT Ile															1248
50		GGG															1296
55		CCT Pro															1344

5		AAG Lys 450															1392
		AAC Asn															1440
10	Gly	CTC Leu	Ser	Lys	Ala 485	Leu	Gly	Ala	Asp	Asp 490	Ser	Tyr	Tyr	Thr	Ala 495	Arg	1488
15	Ser	GCA Ala	Gly	Lys 500	Trp	Pro	Leu	Lys	Trp 505	Tyr	Ala	Pro	Glu	Cys 510	Ile	Asn	1536
20	Phe	CGC	Lys 515	Phe	Ser	Ser	Arg	Ser 520	Asp	Val	Trp	Ser	Tyr 525	Gly	Val	Thr	1584
25	Met	Trp 530	Glu	Ala	Leu	Ser	Tyr 535	Gly	Gln	Lys	Pro	Tyr 540	Lys	Lys	Met		1632
20	Gly 545	CCG	Glu	Val	Met	Ala 550	Phe	Ile	Glu	Gln	Gly 555	Lys	Arg	Met	Glu	Cys 560	1680
30	Pro	CCA Pro	Glu	Cys	Pro 565	Pro	Glu	Leu	Tyr	Ala 570	Leu	Met	Ser	Asp	Cys 575	Trp	1728
35	Ile	TAC	Lys	Trp 580	Glu	Asp	Arg	Pro	Asp 585	Phe	Leu	Thr	Val	Glu 590	Gln	Arg	1776
40	Met	CGA	Ala 595	Сув	Tyr	Tyr	Ser	Leu 600	Ala	Ser	Lys	Val	Glu 605	Gly	Pro	Pro .	1824
45	Gly	AGC Ser 610	Thr	Gln	Lys	Ala	Glu 615	Ala	Ala	Cys	Ala	Trp 620	Asp	Pro	Pro	Val	1872
		ACC Thr															1920
50	ATC	CTG Leu															1968
55		GGC Gly															2016

5		ATC Ile										2064
3		ACC Thr 690					Ser		Tyr			2112
10		AAG Lys										2160
15		GAG Glu								_		2208
20		GAG Glu										2256
25		GGC Gly										2304
		TAC Tyr 770										2352 .
30		AAC Asn										2400
35		AGC Ser										2448
40		GGC Gly										2496
45											CTG Leu	2544
					Ile				Asp		TAC Tyr	2592
50	AAG Lys 865							•				2598

55 (2) INFORMATION FOR SEQ ID NO:111:

203

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 865 amino acids
- (B) TYPE: amino acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

5

55

- (ii) MOLECULE TYPE: protein
- (v) FRAGMENT TYPE: internal
- 10 (xi) SEQUENCE DESCRIPTION: SEQ ID NO:111:

Met Pro Asp Pro Ala Ala His Leu Pro Phe Phe Tyr Gly Ser Ile Ser Arg Ala Glu Ala Glu His Leu Lys Leu Ala Gly Met Ala Asp Gly 15 Leu Phe Leu Leu Arg Gln Cys Leu Arg Ser Leu Gly Gly Tyr Val Leu Ser Leu Val His Asp Val Arg Phe His His Phe Pro Ile Glu Arg Gln 20 Leu Asn Gly Thr Tyr Ala Ile Ala Gly Gly Lys Ala His Cys Gly Pro 70 75 Ala Glu Leu Cys Glu Phe Tyr Ser Arg Asp Pro Asp Gly Leu Pro Cys Asn Leu Arg Lys Pro Cys Asn Arg Pro Ser Gly Leu Glu Pro Gln Pro 25 Gly Val Phe Asp Cys Leu Arg Asp Ala Met Val Arg Asp Tyr Val Arg 120 Gln Thr Trp Lys Leu Glu Gly Glu Ala Leu Glu Gln Ala Ile Ile Ser 135 30 Gln Ala Pro Gln Val Glu Lys Leu Ile Ala Thr Thr Ala His Glu Arg 150 155 Met Pro Trp Tyr His Ser Ser Leu Thr Arg Glu Glu Ala Glu Arg Lys 170 Leu Tyr Ser Gly Ala Gln Thr Asp Gly Lys Phe Leu Leu Arg Pro Arg 35 185 Lys Glu Gln Gly Thr Tyr Ala Leu Ser Leu Ile Tyr Gly Lys Thr Val 200 Tyr His Tyr Leu Ile Ser Gln Asp Lys Ala Gly Lys Tyr Cys Ile Pro 215 40 Glu Gly Thr Lys Phe Asp Thr Leu Trp Gln Leu Val Glu Tyr Leu Lys 230 Leu Lys Ala Asp Gly Leu Ile Tyr Cys Leu Lys Glu Ala Cys Pro Asn 245 250 Ser Ser Ala Ser Asn Ala Ser Gly Ala Ala Ala Pro Thr Leu Pro Ala 45 265 His Pro Ser Thr Leu Thr His Pro Gln Arg Arg Ile Asp Thr Leu Asn 280 Ser Asp Gly Tyr Thr Pro Glu Pro Ala Arg Ile Thr Ser Pro Asp Lys 295 300 50 Pro Arg Pro Met Pro Met Asp Thr Ser Val Tyr Glu Ser Pro Tyr Ser 310 Asp Pro Glu Glu Leu Lys Asp Lys Leu Phe Leu Lys Arg Asp Asn

325

Leu Leu Ile Ala Asp Ile Glu Leu Gly Cys Gly Asn Phe Gly Ser Val

Arg Gln Gly Val Tyr Arg Met Arg Lys Lys Gln Ile Asp Val Ala Ile

		_	355	_				360	_		_		365			
	Lys		Leu	Lys	Gln	Gly	Thr	Glu	Lys	Ala	Asp	Thr	Glu	Glu	Met	Met
		370					375					380				
	Arg	Glu	Ala	Gln	Ile	Met	His	Gln	Leu	Asp	Asn	Pro	Tyr	Ile	Val	Arg
5	385					390					395					400
	Leu	Ile	Gly	Val	Cys	Gln	Ala	Glu	Ala	Leu	Met	Leu	Val	Met	Glu	Met
			-		405					410					415	
	בות	al v	Gly	Glv	Pro	T.e.11	Wie	Lave	Dhe		Val.	Gliv	Lare	Ara		Glu
	AIA	GIY	Cry	420	110	DCu	1110	цya	425	пси	Val	Cry.	Lys	430	014	
40		D	**- 1		2	**- 1	77-	a 1			TT 2 -	a1	**- 1		Mob	C11.
10	iie	Pro		ser.	Asn	val	Ата		Leu	ьeu	HIS	GIN		ser	Mec	GTA.
			435		_			440	_	_			445			
	Met	Lys	Tyr	Leu	Glu	Glu	Lys	Asn	Phe	Val	His	Arg	Asp	Leu	Ala	Ala
		450					455					460				
	Arg	Asn	Val	Leu	Leu	Val	Asn	Arg	His	Tyr	Ala	Lys	Ile	Ser	Asp	Phe
15	465					470					475					480
	Glv	Leu	Ser	Lys	Ala	Leu	Gly	Ala	Asp	Asp	Ser	Tyr	Tyr	Thr	Ala	Arg
	•			-	485		-		-	490		•	-	•	495	_
	Ser	Δla	Glv	Lvs	Trp	Pro	Leu	Lvs	Trp		Ala	Pro	Glu	Cvs	Ile	Asn
	001		1	500				-70	505	-1-				510		
20	Dha	7. ~~	Tare		Ser	Cor				17-1	Tree.	Cor	Т~		Val	Thr
20	Pile	Arg		FIIC	361	261	AIG		web	vai	тър	261		GIY	Val	1111
		_	515		_	_	_	520		_	_		525	<u> </u>	30 - L	•
	Met	_	GIU	Ala	Leu	ser	_	GIY	GIn	ràs	Pro	-	гàг	rys	Met	гÀг
		530	•				535					540				
•	Gly	Pro	Glu	Val	Met	Ala	Phe	Ile	Glu	Gln	Gly	Lys	Arg	Met	Glu	Cys
25	545					550					555					560
	Pro	Pro	Glu	Cys	Pro	Pro	Glu	Leu	Tyr	Ala	Leu	Met	Ser	Asp	Cys	Trp
				_	565				_	570				_	575	
	Tle	Tvr	Lvs	Trp	Glu	Asp	Ara	Pro	Asp	Phe	Leu	Thr	Val	Glu	Gln	Arg
		-3-		580			5		585					590		
30	Mot	7 ~~	λla		Tyr	Tur	Sar	T.011		Car	Laze	Val	G3 u		Dro	Pro
30	Mer	Arg		Cys	TYL	TYL	261	600	AIA	261	пур	Val	605	Gry	110	1.10
		_	595	a 7	-		~ 3			_				D	D	77-7
	GIA		Thr	Gin	Lys	Ата		Ala	Ala	Cys	ΫTα	-	Asp	Pro	Pro	vai
		610		_			615	_			_	620			-	_
	Ala	Thr	Met	Val	Ser	Lys	Gly	Glu	Glu	Leu	Phe	Thr	Gly.	Val	Val	Pro
35	625					630					635					640
	Ile	Leu	Val	Glu	Leu	Asp	Gly	Asp	Val	Asn	Gly	His	Lys	Phe	Ser	Val
					645					650					655	
	Ser	Gly	Glu	Gly	Glu	Gly	Asp	Ala	Thr	Tyr	Gly	Lys	Leu	Thr	Leu	Lys
		-		660		_	-		665	-	-	-		670		
40	Phe	Tle	Cvs	Thr	Thr	Glv	Lvs	Leu	Pro	Val	Pro	Trp	Pro	Thr	Leu	Val
			675			1	7 -	680					685			
	Thr	Thr		Thr	Tyr	Glv	Wa l		Cvc	Dhe	Car	λνα		Pro	Δen	His
	1111		Deu	1111	TYL	Gry		GIII	СуБ	FIIC	Ser		IYL	110	rob	1115
		690	~ 1	***		5 1	695	_	_			700	a 1	a 3		17. 7
		ГÀв	Gin	Hls	Asp		Pne	гÀг	ser	Ата		Pro	GIU	GTÅ	Tyr	
45	705				_	710	_				715					720
	Gln	Glu	Arg	Thr	Ile	Phe	Phe	Lys	Asp	Asp	Gly	Asn	Tyr	Lys	Thr	Arg
					725					730					735	
	Ala	Glu	Val	Lys	Phe	Glu	Gly	Asp	Thr	Leu	Val	Asn	Arg	Ile	Glu	Leu
				740					745					750		
50	Lvs	Glv	Ile	asa	Phe	Lvs	Glu	Asp	Glv	Asn	Ile	Leu	Glv	His	Lys	Leu
	-1-	1	755	2				760	1				765		-	
	G3 11	ጥህን		ጥነታም	Asn	Ser	ніс		17 = 1	ጥ፣ታ	Tle	Met		Aen	Tive	Gln
	GIU	770		- y -			775	Hall	val	* A T		780	HIG	p	-73	
	v		01	T7 -	T	37-7		DL -	T	77.	7		7	т1-	01	7 ~~
	-	ASN	GIÀ	тте	Lys		Asn	rne	ràs	тте	_	nls	ASD	тте	GIU	
55	785				_	790					795					800
	Gly	Ser	Val	Gln	Leu	Ala	Asp	His	Tyr	Gln	Gln	Asn	Thr	Pro	Ile	Gly

									•	203								
					805					810					815			
	Asp	Gly	Pro	Val 820		Leu	Pro	qaA	Asn 825		Tyr	Leu	Ser	Thr 830		Ser		
5	Ala	Leu	Ser 835		Asp	Pro	Asn	Glu 840		Arg	Asp	His	Met 845		Leu	Leu		
	Glu	Phe 850		Thr	Ala	Ala	Gly 855		Thr	Leu	Gly	Met 860		Glu	Leu	Tyr		
	Lys	650					655					000						
10	865		(2)	INE	-CDM7	TTON		0 000	, TD	NO - 1	12.							
	:		(2)	-11/1	ORM	LITON	· FOF	COEC	עב ג	MO: 1	.14.							
15		()	(A) (B) (C)	EQUEN LENG TYPE STRA TOPO	TH: : nu ANDEI	1635 iclei NESS	bas c ac s: si	e pa id ingle	irs									
20				OLEC FEATU		TYPE	E: cI	AAG										
25			(B)	NAN LOC OTI	CATIO	ON: 3	LI	1632 ION:										
		. (3	(i) S	SEQUE	ENCE	DESC	CRIPT	NOI	: SE() ID	NO:	112:						
30		GAG Glu														Gly	48	
		GTG Val															.96	
35		AAA Lys															144	
40		CGA Arg 50													_	_	192	٠.
45		CTG Leu															240	
50		TTT															288	
55		GGC													Leu		336	
JJ	CAG	GGC	CTA	GCT	TTC	TGC	CAT	TCT	CAT	CGG	GTC	CTC	CAC	CGA	GAC	CTT	384	205

	Gln	Gly	Leu 115	Ala	Phe	Cys	His	Ser 120	His	Arg	Val	Leu	His 125	Arg	Asp	Leu		
5				AAT Asn													432	
10				CTA Leu													480	
15				GTG Val												GGC Gly	528	
				TAT Tyr 180													576	
20				ATG Met													624	
25				CTC Leu													672	
30				CCA Pro													720	
35				GCC Ala													768	
				CGG Arg 260												AAC Asn	816	
40				TCG Ser										Phe			864	
45		`		CCA Pro													912	
50				AGC Ser													960	•
E E				CTG Leu													1008	
55	GGC	GAG	GGC	GAG	GGC	GAT	GCC	ACC	TAC	GGC	AAG	CTG	ACC	CTG	AAG	TTC	1056	206

207

									•	201								
	Gly	Glu	Gly	Glu 340	Gly	Asp	Ala	Thr	Tyr 345	Gly	Lys	Leu	Thr	Leu 350	Lys	Phe		•
5		TGC Cys																1104
10		CTG Leu 370																1152
45		CAG Gln																1200
15		CGC Arg																1248
20		GTG Val																1296
25		ATC Ile																1344
30		AAC Asn 450																1392
35		GGC Gly														_		1440
33		GTG Val				Asp					Asn							1488
40		CCC Pro																1536
45		AGC Ser																1584
50		GTG Val 530														AAG Lys	Т	1633
	AA																	1635

(2) INFORMATION FOR SEQ ID NO:113:

(i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 544 amino acids
- (B) TYPE: amino acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

- (ii) MOLECULE TYPE: protein
 (v) FRAGMENT TYPE: internal
- (xi) SEQUENCE DESCRIPTION: SEQ ID NO:113:

10																
	1				5					10				Thr	15	
•				20			•		25					Val 30		
15	Lys	Lys	Ile 35	Arg	Leu	qaA	Thr	Glu 40	Thr	Glu	Gly	Val	Pro 45	Ser	Thr	Ala
	Ile	Arg 50	Glu	Ile	Ser	Leu	Leu 55	Lys	Glu	Leu	Asn	His 60	Pro	Asn	Ile	Val
20	65			_		70					75			Leu		80
					85				_	90				Ser	95	
		_		100					105					Gln 110		
25			115					120					125	Arg		
	-	130					135					140		Lys		
30	145		_			150			_		155			Thr		160
					165					170				Leu	175	
				180					185				•	Gly 190		
35			195					200					205	Asp		
		210					215					220		Pro		
40	225					230					235					Phe 240
					245					250				Pro	255	
				260					265					Asp 270		
45			275					280					285			Asp
		290					295			•		300				Ala
50	305					310					315					11e 320
					325					330)				335	
				340					345					350		Phe
55	Ile	Cys	Thr 355		GIÀ	гус	Leu	360		Pro	ırp	Pro	365		val	Thr

	Thr	Leu 370	Thr	Tyr	Gly	Val	Gln 375	Сув	Phe	Ser	Arg	Tyr 380	Pro	Asp	His	Met	•
	Lys 385	Gln	His	Asp	Phe	Phe 390	Lys	Ser	Ala	Met	Pro 395	Glu	Gly	Tyr	Val	Gln 400	
_			m1	-7.	D1		-			~7		-			_		
5		Arg			405				• -	410		•			415		
	Glu	Val	Lys	Phe 420	Glu	Gly	Asp	Thr	Leu 425	Val	Asn	Arg	Ile	Glu 430	Leu	Lys	•
10	Gly	Ile	Asp 435	Phe	Lys	Glu	Asp	Gly 440	Asn	Ile	Leu	Gly	His 445	Lys	Leu	Glu	
	Tyr	Asn 450	Tyr	Asn	Ser	His	Asn 455		Tyr	Ile	Met	Ala 460	Asp	Lys	Gln	Lys	
	7.00	Gly	Tla	Laze	17 = 1	Acn		Larc	T10	7~~	Wic		Tla	Glu.	λαν	Gly	
	465					470					475					480	
15	Ser	Val	Gln	Leu	A1a 485	Asp	His	Tyr	Gļn	Gln 490	Asn	Thr	Pro	Ile	Gly 495	Asp	
	Gly	Pro	Val	Leu 500	Leu	Pro	Asp	Asn	His 505	Tyr	Leu	Ser	Thr	Gln 510	Ser	Ala	
20	Leu	Ser	Lys 515	Asp	Pro	Asn	Glu	Lys 520	Arg	Asp	His	Met	Val 525	Leu	Leu	Glu	
20	ni.	17- 7		7 7 a	. הוה	~1	т1.		7	~ 1	Mak	7		T 011	m	T	
	Pne	Val 530	IIII	Ald	Ата	GIY	535	Inr	Leu	GIY	Met	540	Giu	ren	TYL	гуз	
			(2)) IN	FORM	ATIOI	1 FOI	R SE	Q ID	NO:	114:						
25																	
		(:	i) Si	EQUE	VCE (CHAR	ACTE	RIST:	ICS:								
			(A)	LEN	GTH:	163	ba:	se pa	airs								
			(B)	TYP	E: ni	icle:	ic a	cid									
			(C)	STR	ANDEI	ONES	S: \$:	ingl	e .								
30			(D)	TOP	DLOG	Y: 1:	inear	r									
				•													
				MOLE FEAT		TYP	E: Cl	ONA									•
		٠.															
35			(A)	IAN (ME/KI	EY: (Codi	ng S	eque	nce							
			(B)	LO	CATIO	ON:	1;	1632	•								
			(D)	OT	HER :	INFO	TAMS	ON:									
		(:	ki) (SEQUI	ENCE	DES	CRIP	rion	: SE	O ID	NO:	114:	•				
40				_						_							
	ATG	GTG	AGC	AAG	GGC	GAG	GAG	CTG	TTC	ACC	GGG	GTG	GTG	CCC	ATC	CTG	48
	Met	Val	Ser	Lys	Gly	Glu	Glu	Leu	Phe	Thr	Gly	Val	Val	Pro	Ile	Leu	
	1				5					10	-				15		
45	GTC	GAG	CTG	GAC	GGC	GAC	GTA	AAC	GGC	CAC	AAG	TTC	AGC	GTG	TCC	GGC	96
_		Glu														_	
	•			20	1				25		ביים			30		2	
		GGC															144
50	Glu	Gly	Glu	Gly	Asp	Ala	Thr	Tyr	Gly	Lys	Leu	Thr	Leu	Lys	Phe	Ile	
			35					40					45				
	TGC	ACC	ACC	GGC	AAG	CTG	ccc	GTG	CCC	TGG	CCC	ACC	CTC	GTG	ACC	ACC	192
	Cys	Thr	Thr	Gly	Lys	Leu	Pro	Val	Pro	Trp	Pro	Thr	Leu	Val	Thr	Thr	
55		50					55					60					

																	•
									AGC Ser								240
5									ATG								288
	Gln	His	qaA	Phe		Lys	Ser	Ala	Met		Glu	Gly	Tyr	Val		Glu	
					85		•			90					95		
	CGC	ACC	ATC	TTC	TTC	AAG	GAC	GAC	GGC	AAC	TAC	AAG	ACC	ccc	GCC	GAG	336
10									Gly								
				100					105					110			
	ama	D D C	mma	CNC	000	C D C	7.00	ama.	ama	220		3 m.C	G 2 G	CIE/C	220	000	204
									Val							GGC	384
15	• • • •		115		OL7			120	• • • • • • • • • • • • • • • • • • • •		•••		125	204	2,5	OL y	
									ATC								432
	116	130	Pne	гув	GIU	Авр	135		Ile	Leu	GIY	140	гув	ьeu	GIU	Tyr	
20																	
									ATC							-	480
		Tyr	Asn	Ser	His		Val	Tyr	Ile	Met		Asp	Lys	Gln	Lys		
	145					150					155					160	
25	GGC	ATC	AAG	GTG	AAC	TTC	AAG	ATC	CGC	CAC	AAC	ATC	GAG	GAC	GGC	AGC	528
	Gly	Ile	Lys	Val		Phe	Lys	Ile	Arg		Asn	Ile	Glu	Asp	_	Ser	
					165					170					175		
	GTG	CAG	CTC	GCC	GAC	CAC	TAC	CAG	CAG	AAC	ACC	ccc	ATC	GGC	GAC	GGC	576
30									Gln								
				180	•				185					190			
	ccc	CTC	СТС	CTG	ccc	GAC	AAC	כאכ	TAC	CTG	NGC	אככ	CAG	TCC	GCC	СТС	624
									Tyr								024
35			195			•		200	-				205				
			~~~												~~~	<b>****</b>	600
									GAT Asp								672
	501	210	p	110	71011	014	215	n. 9	vab	1113	1.00	220	100	200		1110	
40																	
									GGC								720.
	225	Tnr	Ala	Ala	GIÀ	11e 230	Thr	Leu	Gly	Met	Asp 235	Glu	Leu	Tyr	rys	ser 240	
•	223					230					233					240	
45	GGA	CTC	AGA	TCT	CGA	GCC	ATG	GAG	AAC	TTC	CAA	AAG	GTG	GAA	AAG	ATC	768
	Gly	Leu	Arg	Ser	_	Ala	Met	Glu	Asn		Gln	Lys	Val	Glu		Ile	
					245					250					255		
	GGA	GAG	GGC	ACG	TAC	GGA	GTT	GTG	TAC	AAA	GCC	AGA	AAC	AAG	TTG	ACG	816
50									Tyr							_	
				260					265					270			
	CCA	GNG	CITIC	GTG	GCG.	CTTT	מממ	ממת	ATC	000	משת	CAC	א כיייי	GAG	א כיייי	GAG	864
									Ile								004
55	- 3		275					280		J.			285	•			

			AGT Ser							912
	5		AAT Asn							960
1	0		CTG Leu							1008
1	°. 5		TCT Ser 340							1056
. 2	0		CAG Gln							1104
-			CGA Arg						GAG Glu	1152
2	5		AAG Lys							1200
3	0		ACT Thr							1248
3	5		CTC Leu 420							1296
4	O		GGC Gly							1344
*	U		GAT Asp							1392
4	5		CCA Pro							1440
5	0		CCA Pro							1488
. 5	5		CCC Pro 500							1536

									•	212		•						
								CGG Arg 520										1584
5								ACC Thr									T	1633
	GA																	1635
10			(2)	INF	ORMA	ATION	FOF	SEC	) ID	NO:1	.15:							
15		(i	(A)		TH:	544	amir	RISTI 10 ac									•	
15			(C)		NDEI	DNESS	3: si	ingle	<b>2</b>									
20							_	rotei terna										
				_				rion :		,							•	·
25		Val	Ser	Lys	Gly 5	Glu	Glu	Leu	Phe	Thr 10	Gly	Val	Val	Pro	11e 15	Leu		
25	1 Val	Glu	Leu	Asp 20	_	Asp	Val	Asn	Gly 25		Lys	Phe	Ser	Val 30	-	Gly		
	Glu	Gly	Glu 35		Asp	Ala	Thr	Tyr 40	Gly	Lys	Leu	Thr	Leu 45	Lys	Phe	Ile		
30	Сув	Thr 50	Thr	Gly	Lys	Leu	Pro 55	Val	Pro	Trp	Pro	Thr 60	Leu	Val	Thr	Thr		
	65					70		Phe			75					80		
35			-		85			Ala		90					95			
				100				Asp Leu	105					110				
		_	115					120					125					
40		130					135					140						
		Tyr	Asn	Ser	His	Asn 150	Val	Tyr	Ile	Met	Ala 155		Lys	Gln	Lys	Asn 160		
	145 Gly	Ile	Lys	Val	Asn		Lys	Ile	Arg	His			Glu	Asp	Gly			
45	-				165			Gln		170					175			
				180				His	185					190				
50			195					200 Arg					205					
		210					215					220						
	225					230			1		235			•	•	240		
55	Gly	Leu	Arg	Ser	Arg 245	Ala	Met	Glu	Asn	Phe 250		Lys	Val	Glu	Lys 255		:	
	Gly	Glu	Gly	Thr	Tyr	Gly	Val	Val	Tyr	Lys	Ala	Arg	Asr.	Lys	Lei	Thr	•	

				260					265					270			•
	Gly	Glu	Val 275	Val	Ala	Leu	Lys	Lys 280	Ile	Arg	Leu	Asp	Thr 285	Glu	Thr	Glu	
5	Gly	Val 290	Pro	Ser	Thr	Ala	Ile 295	Arg	Glu	Ile	Ser	Leu 300	Leu	Lys	Glu	Leu	
		His	Pro	Asn	Ile		Lys	Leu	Leu	Asp		Ile	His	Thr	Glu		
•	305 Lys	Leu	Tyr	Leu	Val	310 Phe	Glu	Phe	Leu	His	315 Gln	Asp	Leu	Lys	Lys	320 Phe	
10			21-		325	T	mlass	<b>63</b>	-1.	330		_	_		335	<b>a</b>	
10		Asp		340				_	345					350	-		
		Leu	355					360				_	365				
15	·Val	Leu 370	His	Arg	Asp	Leu	Lys 375	Pro	Gln	Asn	Leu	Leu 380	Ile	Asn	Thr	Glu	
	Gly	Ala	Ile	Lys	Leu	Ala		Phe	Gly	Leu	Ala		Ala	Phe	Gly	Val	
	385 Bro	Val	Ara	Thr	Tur	390	Hic	Glu	Wa l	Val	395	Len	Trn	Tur	Ara	400 Ala	
	PIO	Val	Arg	1111	405		nis		vai	410	1111	рец	тър	ıyı	415	ATO	
20	Pro	Glu	Ile	Leu 420	Leu	Gly	Ser	Lys	Tyr 425	Tyr	Ser	Thr	Ala	Val 430	qaA	Ile	
•	Trp	Ser	Leu 435	Gly	Cys	Ile	Phe	Ala 440	Glu	Met	Val	Thr	Arg 445	Arg	Ala	Leu	
25	Phe	Pro 450	Gly	qaA	Ser	Glu	Ile 455	Asp	Gln	Leu	Phe	Arg 460	Ile	Phe	Arg	Thr	
		Gly	Thr	Pro	Asp			Val	Trp	Pro	Gly		Thr	Ser	Met	Pro	
	465					470					475					480	
	Asp	Tyr	Lys	Pro	Ser 485	Phe	Pro	Lys	Trp	Ala 490	Arg	Gln	Asp	Phe	Ser 495	Lys	
30	Val	Val	Pro	Pro 500	Leu	Asp	Glu	Asp	Gly 505	Arg	Ser	Leu	Leu	Ser 510	Gln	Met	
	Leu	His	Tyr 515	Asp	Pro	Asn	Lys	Arg 520	Ile	Ser	Ala	Lys	Ala 525	Ala	Leu	Ala	
25	His	Pro	Phe	Phe	Gln	Asp			Lys	Pro	Val			Leu	Arg	Leu	
35		530					535					540					
			(2)	INI	FORM	10ITA	1 FOI	R SE	Q ID	NO:	116:						
40		( :		EQUE													
40				LENG					airs								
				STR					_								
				TOP				_	=								
45		14	: 4 \ R	OLE	ים דווי	ומעת	7. at	<b>7877</b>									
40				FEAT		1111	5: CI	JNA								•	
			/n \	NT 70 B	4T2 / 7/1	7V. /											
				NAM LOC				_	eque	nce							
50				OTI										•			
		(ż	ci) S	EQUI	ENCE	DESC	CRIP	rion	: SE	αI Ç	NO:	116:					
	ATG	GTG	AGC ·	AAG	GGC	GAG	GAG	CTG	TTC	ACC	GGG	GTG	GTG	CCC	ATC	CTG	48
55	Met				Gly										Ile	Leu	
	1				- 5					10					15		

	•			GGC Gly											96
5	a.a	222	an a	03 M	000		m> 0		ama	3.00	ama.		mma	1 ma	244
				GAT Asp						Thr		•			144
10				AAG Lys											192
15				GTG Val											240
20				TTC Phe 85											288
0.5				TTC Phe									_	_	336
25				GGC Gly										_	384
30				GAG Glu											432
35				CAC His											480
40				AAC Asn 165	Phe	Lys	Ile	His	Asn						528
45				GAC Asp											576
40				CCC Pro											624
50				AAC Asn											672
55		Thr		GGG Gly											720

. 5															CGA Arg 255		768
															GTC Val		816
10															TTC Phe		864
15															CAG Gln		912
20															ACT Thr		960
25	Thr	Glu	Leu	Val	Glu 325	Tyr	Tyr	Thr	Gln	Gln 330	Gln	Gly	Val	Leu	CAG Gln 335	Asp	1008
															TCC Ser		1056
30															CAG Gln		1104
35	Glu	Thr 370	Leu	Leu	Gln	Ala	Lys 375	Gly	Glu	Pro	Trp	Thr 380	Phe	Leu	GTG Val	Arg	1152
40	Glu 385	Ser	Leu	Ser	Gln	Pro 390	Gly	Asp	Phe	Val	Leu 395	Ser	Val	Leu	AGT Ser	Asp 400	1200
45															ATC Ile 415		1248
															ACC Thr		1296
50															ATT Ile		1344
55															GCC Ala		1392

5		GTG Val															1440
		CAG Gln															1488
10		AGT Ser															1536
15		CAG Gln															1584
20		TTT Phe 530															1632
25		GGG Gly															1680
		CCT Pro															1728
30		GCC Ala															1776
35		GTC Val															1824
40	Cys	GTC Val 610				Pro											1872
45	TAC Tyr 625	TCT Ser	GTG Val	ACC Thr	AAC Asn	TGC Cys 630	GGG Gly	GAG Glu	CAT His	GAC Asp	ACA Thr 635	ACC Thr	GAA Glu	TAC Tyr	AAA Lys	CTC Leu 640	1920
		ACC Thr															1968
50	ATC Ile	TGG Trp	CAT His	TAC Tyr 660	CAG Gln	TAC Tyr	CTG Leu	AGC Ser	TGG Trp 665	CCC Pro	GAC Asp	CAT His	GGG Gly	GTC Val 670	CCC Pro	AGT Ser	2016
55	GAG Glu	CCT Pro	GGG Gly 675	GGT Gly	GTC Val	CTC Leu	AGC Ser	TTC Phe 680	CTG Leu	GAC Asp	CAG Gln	ATC Ile	AAC Asn 685	CAG Gln	CGG Arg	CAG Gln	2064

5												CAC His 700					2112
												ATG Met					2160
10												ATC Ile					2208
15	Gln	Met	Val	Arg 740	Ala	Gln	Arg	Ser	Gly 745	Met	Val	CAG Gln	Thr	Glu 750	Ala	Gln	2256
20	Tyr	Lys	Phe 755	Ile	Tyr	Val.	Ala	Ile 760	Ala	Gln	Phe	ATT	Glu 765	Thr	Thr	Lys	2304
25												CAG Gln 780					2352
												GCC Ala					2400
30												TAT Tyr					2448
35					Arg					Lys					Ala	GAC Asp	2496
40		GAG Glu										TGA					2532
			(2	) IN	FORM	OITA	n fo	R SE	Q ID	NO:	117:						
45		(	(A) (B) (C)	LEN TYP STR	GTH: E: a ANDE	843 mino DNES	ACTE ami aci S: s inea	no a d ingl	cids								
50			ii)	MOLE	CULE	TYP	E: p	rote									
55												117:					
	Met	. Val	Ser	Lys	Gly	Glu	Glu	Lev	Phe	Thr	Gly	/ Val	l Val	Pro	ıl.	Leu	0.

	1				5					10					15	
	Val	Glu	Leu	Asp 20	Gly	qaA	Val	Asn	Gly 25	His	Lys	Phe	Ser	Val 30	Ser	Gly
5	Glu	Gly	Glu 35	Gly	Asp	Ala	Thr	Tyr 40	Gly	Lys	Leu	Thr	Leu 45	Lys	Phe	Ile
	Cys	Thr 50	Thr	Gly	Lys	Leu	Pro 55	Val	Pro	Trp	Pro	Thr 60	Leu	Val	Thr	Thr
•	Leu 65		Tyr	Gly	Val	Gln 70	Cys	Phe	Ser	Arg	Tyr 75	Pro	qaA	His	Met	Lys 80
10		His	Asp	Phe	Phe 85		Ser	Ala	Met	Pro 90		Gly	Tyr	Val	Gln 95	Glu
*	Arg	Thr	Ile	Phe 100	Phe	Lys	Asp	Asp	Gly 105	Asn	Tyr	Lys	Thr	Arg 110	Ala	Glu
	Val	Lvs	Phe		Glv	Asp	Thr	Len		Asn	Ara	Tle	Glu	Leu	Lvs	Glv
15			115		_	_		120					125			
		130					135					140		Leu		
00	145	_				150					155			Gln		160
20	-				165					170				Asp	175	
				180	_				185					Gly 190		
25			195					200					205	Ser		
		210					215					220		Leu		
	225				_	230			_		235			Tyr		240
30	_				245		•			250				His	255	
				260					265					Gly 270		
35	_		275					280					285	Asp		
		290					295		•			300		Ile		
	305					310			_		315			Ala		320
40					325					330				Leu	335	
	_	_	_	340					345	_				Cys 350		
45			355		_		_	360	_			٠	365	Gly		
•	Glu	Thr 370	Leu	Leu	Gln	Ala	Lys 375	Gly	Glu	Pro	Trp	Thr 380		Leu	Val	Arg
•	Glu 385		Leu	Ser	Gln	Pro 390	Gly	Asp	Phe	Val	Leu 395	Ser	Val	Leu	Ser	Asp 400
50	Gln	Pro	Lys	Ala	Gly 405	Pro	Gly	Ser	Pro	Leu 410		Val	Thr	His	1le 415	
	Val	Met	Cys	Glu 420	Gly	Gly	Arg	Tyr	Thr 425	Val	Gly	Gly	Leu	Glu 430		Phe
55	Asp	Ser	Leu 435	Thr	Asp	Leu	Val	Glu 440	His	Phe	Lys	Lys	Thr 445	Gly	Ile	Glu
	Glu	Ala		Gly	Ala	Phe	Val	Tyr	Leu	Arg	Gln	Pro	Tyr	Tyr	Ala	Thr

WO 98/45704 PCT/DK98/00145

219

		450					455					460				
	Arg 465	Val	Asn	Ala	Ala	Asp 470	Ile	Glu	Asn	Arg	Val 475	Leu	Glu	Leu	Asn	Lys 480
5					485				Lys	490					495	
٠				500					Lуs 505					510		
			515					520	Lys	•			525			
10		530					535		Leu			540				
	545					550			Asn		555					560
15	_				565		_		Tyr	570				_	575	
				580				_	Gln 585			_		590		
			595					600	Glu			_	605			_
20		610					615		Gly			620		•		
	625					630			His		635					640
25					645				Asp	650	-	_			655	•
				660					Trp 665 Leu					670		
30			675					680	Ile	_			685		_	
00		690					695		Val			700	•			
	705					710			Asp		715					720
35					725		-	-	Gly	730	_			_	735	
				740			_		745 Ala					750		
40			755					760	Gln				765			
		770				•	775		Met	-	_	780				
	785					790			Glu		795					800
45					805				Val	810		_			815	
				820					825 Lys			GIII	Arg	830	AIG	vsb
50	<i>_</i> , 0	014	835	JUL	275	- y		840	ביים	ur 3	nys					
			/~ `	****												

(2) INFORMATION FOR SEQ ID NO:118:

- (i) SEQUENCE CHARACTERISTICS:
  - (A) LENGTH: 2562 base pairs
  - (B) TYPE: nucleic acid

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(C) STRANDEDNESS: single

WO 98/45704 PCT/DK98/00145

220 (D) TOPOLOGY: linear (ii) MOLECULE TYPE: cDNA (ix) FEATURE: 5 (A) NAME/KEY: Coding Sequence (B) LOCATION: 1...2559 (D) OTHER INFORMATION: 10 (xi) SEQUENCE DESCRIPTION: SEQ ID NO:118: ATG CTG TCC CGT GGG TGG TTT CAC CGA GAC CTC AGT GGG CTG GAT GCA 48 Met Leu Ser Arg Gly Trp Phe His Arg Asp Leu Ser Gly Leu Asp Ala 1 5 10 15 GAG ACC CTG CTC AAG GGC CGA GGT GTC CAC GGT AGC TTC CTG GCT CGG 96 Glu Thr Leu Leu Lys Gly Arg Gly Val His Gly Ser Phe Leu Ala Arg 20 CCC AGT CGC AAG AAC CAG GGT GAC TTC TCG CTC TCC GTC AGG GTG GGG 144 Pro Ser Arg Lys Asn Gln Gly Asp Phe Ser Leu Ser Val Arg Val Gly 40 -GAT CAG GTG ACC CAT ATT CGG ATC CAG AAC TCA GGG GAT TTC TAT GAC 192 25 Asp Gln Val Thr His Ile Arg Ile Gln Asn Ser Gly Asp Phe Tyr Asp 55 CTG TAT GGA GGG GAG AAG TTT GCG ACT CTG ACA GAG CTG GTG GAG TAC 240 Leu Tyr Gly Gly Glu Lys Phe Ala Thr Leu Thr Glu Leu Val Glu Tyr 30 TAC ACT CAG CAG GGT GTC CTG CAG GAC CGC GAC GGC ACC ATC ATC 288 Tyr Thr Gln Gln Gly Val Leu Gln Asp Arg Asp Gly Thr Ile Ile 85 90 35 CAC CTC AAG TAC CCG CTG AAC TGC TCC GAT CCC ACT AGT GAG AGG TGG 336 His Leu Lys Tyr Pro Leu Asn Cys Ser Asp Pro Thr Ser Glu Arg Trp 100 105 40 TAC CAT GGC CAC ATG TCT GGC GGG CAG GCA GAG ACG CTG CTG CAG GCC 384 Tyr His Gly His Met Ser Gly Gly Gln Ala Glu Thr Leu Leu Gln Ala 120 AAG GGC GAG CCC TGG ACG TTT CTT GTG CGT GAG AGC CTC AGC CAG CCT 432 45 Lys Gly Glu Pro Trp Thr Phe Leu Val Arg Glu Ser Leu Ser Gln Pro 130 135 140 GGA GAC TTC GTG CTT TCT GTG CTC AGT GAC CAG CCC AAG GCT GGC CCA Gly Asp Phe Val Leu Ser Val Leu Ser Asp Gln Pro Lys Ala Gly Pro 50 145 150 160 GGC TCC CCG CTC AGG GTC ACC CAC ATC AAG GTC ATG TGC GAG GGT GGA Gly Ser Pro Leu Arg Val Thr His Ile Lys Val Met Cys Glu Gly Gly 165

220

CGC TAC ACA GTG GGT TTG GAG ACC TTC GAC AGC CTC ACG GAC CTG

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										~~ '							
	Arg	Tyr	Thr	Val 180	Gly	Gly	Leu	Glu	Thr 185	Phe	Asp	Ser	Leu	Thr 190	-	Leu	
	СТД	GAG	כאד	יייי	AAG	AAG	ACG	GGG	א יייי	GAG	GAG	GCC	TCA	CCC	GCC	יווייווי	624
5					Lys												024
		0	195		-,-			200	110	014	oru.	7.10	205	CII		2.1.0	
	GTC	TAC	CTG	CGG	CAG	CCG	TAC	TAT	GCC	ACG	AGG	GTG	AAT	GCG	GCT	GAC	672
					Gln												
10		210					215	•			J	220				•	
					GTG												720
		Glu	Asn	Arg	Val		Glu	Leu	Asn	Lys	Lys	Gln	Glu	Ser	Glu	qaA	
45	225					230					235					240	
15	202	CCC	אאמ	CCT	~~~		TCC	C 7 C	a	mmm	d a c	3.00	mma	a. a	330	G3.G	7.60
					GGC Gly												768
	1111	лти	2,5	ALU	245	1110	115	GIU	Giu	250	GIU	SEL	пси	GIII	255	GIII	
20	GAG	GTG	AAG	AAC	TTG	CAC	CAG	CGT	CTG	GAA	GGG	CAG	CGG	CCA	GAG	AAC	816
	Glu	Val	Lys	Asn	Leu	His	Gln	Arg	Leu	Glu	Gly	Gln	Arg	Pro	Glu	Asn	
				260					265					270			
25					CGC												. 864
20	пув	Gry	275	ASII	Arg	ıyı	пуз	280	TIE	пеп	PIO	PHE	285	птв	Set	Arg	
								200					203				
	GTG	ATC	CTG	CAG	GGA	CGG	GAC	AGT	AAC	ATC	CCC	GGG	TCC	GAC	TAC	ATC	912
	Val		Leu	Gln	Gly	Arg	Asp	Ser	Asn	Ile	Pro	Gly	Ser	Asp	Tyr	Ile	
30		290			,		295					300					
	אמע	ccc	7 7 C	<b>ምአ</b> ረገ	ATC	א א פי	770	030	CTC	CITI N	000	aam	C A M	CNC	770	O C TT	0.00
					Ile												960
	305			-1-		310		0	ے د	200	315		1105		*****	320	
35																	•
	AAG	ACC	TAC	ATC	GCC	AGC	CAG	GGC	TGT	CTG	GAG	GCC	ACG	GTC	AAT	GAC	1008
	Lys	Thr	Tyr	Ile	Ala	Ser.	Gln	Gly	Cys	Leu	Glu	Ala	Thr	Val		Asp	
	•				325					330					335		
40	TTC	TCC	CAG	እ ፕር	GCG	ጥርር	CNG	CNC	אאכי	NGC	CCT	CTC	አጥሮ	CTC	አጥር	NCC.	1056
40					Ala												1030
				340			·		345	501	y	VU.		350			
	ACC	CGA	GAG	GTG	GAG	AAA	GGC	CGG	AAC	AAA	TGC	GTC	CCA	TAC	TGG	CCC	1104
45	Thr	Arg	Glu	Val	Glu	Lys	Gly	Arg	Asn	Lys	Cys	Val	Pro	Tyr	Trp	Pro	
			355					360					365				
	G) C	CTC	aac	አጥሮ	CAG	CCT	COM	יים איים	000	000	mz c	m Orri	ama	אכיכ	א א מ	TCC	1150
					Gln												1152
50	-1u	370	1			****	375	- 7 -	CIY	110	- Y -	380	Val		47211	-, s	
		-					_										
					ACA												1200
		Glu	His	Asp	Thr		Glu	Tyr	Lys	Leu	_	Thr	Leu	Gln	Val		
EF	385					390					395					400	
55	cca	CTC	CAC	ת את ת	CCN	GNG	CTC	א מונה ע	000	<b></b>	N m ~	TTCC	(13 m	mn a	<b>CD</b> CD	<b>ምእ</b> ር	1040
	درن	CIG	GAC	WWI	GGA	GAL	C16	AIT	دين	GAG	ATC	نان1	CAT	IAC	CAG	IAC	1248
																_	•

WO 98/45704 PCT/DK98/00145

										<b>444</b>							
	Pro	Leu	Asp	Asn	Gly 405	Asp	Leu	Ile	Arg	Glu 410	Ile	Trp	His	Tyr	Gln 415	Tyr	
	CTG	AGC	TGG	CCC	GAC	СУТ	GGG	CTC	CCC	λст	GVG	CCT	GGG	CCT	CTC	כתכ	1296
5					Asp												1290
	אפר	ጥጥር	СТС	GAC	CAG	እ TC	A A C	CAG	ccc	CAG	CNN	. አርሞ	כיינים	CCT	CNC	GCA	1344
					Gln												1344
10	501	1110	435		<b>-</b>			440	,,,,,		OTU	JCI	445	110	1120	Alu	
	GGG	CCC	ATC	ATC	GTG	CAC	TGC	AGC	GCC	GGC	ATC	GGC	CGC	ACA	GGC	ACC	1392
	Gly	Pro	Ile	Ile	Val	His	Cys	Ser	Ala	Gly	Ile	Gly	Arg	Thr	Gly	Thr	
		450					455					460					
15		•															
			_		GAC												1440
		Ile	Val	Ile	Asp		Leu	Met	Glu	Asn		Ser	Thr	Lys	Gly		
	465					470					475	•				480	
20	CAC	TOT	GNC	א תיתי	GAC	አጥሮ	מאפ	አአሮ	א כיכי	איזיכי	כאכ	איזיכי	CTC	CCC	ccc	C) C	1488
20					Asp												1400
	ASP	Cyb	upp		485		01	בעם	1111	490	GIII	1100	vaı	<b>71.</b> 9	495	OIII	
						•											
	CGC	TCG	GGC	ATG	GTG	CAG	ACG	GAG	GCG	CAG	TAC	AAG	TTC	ATC	TAC	GTG	1536
25	Arg	Ser	Gly	Met	Val	Gln	Thr	Glu	Ala	Gln	Tyr	Lys	Phe	Ile	Tyr	Val	
				500					505					510			•
					TTC												1584
00	Ala	Ile		Gln	Phe	Ile	Glu		Thr	Lys	Lys	Lys		Glu	Val	Leu	
30			515					520					525				
	CAG	TCG	CAG	DAG	GGC	CAG	GAG	TCG	GAG	TAC	GGG	ממ	ΔTC	ACC	TAT	CCC	1632
					Gly												
		530		-1-	1		535			-1-	1	540					
35																	
	CCA	GCC	ATG	AAG	AAT	GCC	CAT	GCC	AAG	GCC	TCC	CGC	ACC	TCG	TCC	AAA	1680
	Pro	Ala	Met	Lys	Asn	Ala	His	Ala	Lys	Ala	Ser	Arg	Thr	Ser	Ser	Lys	
	545					550					555					560	
40	a. a	220	<b>C3.C</b>	C 3 F	ama	<b></b>	~~~		ama	a. a	3 CM			220	200	C N C	1700
40					GTG Val												1728
	nis	пуъ	Gru	Asp	565	IÀT	GIU	ASII	пеп	570	1111	пåа	ASII	пуъ	575	GIU	
					303					370					3,3		
	GAG	AAA	GTG	AAG	AAG	CAG	CGG	TCA	GCA	GAC	AAG	GAG	AAG	AGC	AAG	GGT	1776
45					Lys												
		-		580	•		_		585	•	•		•	590	-	-	
	TCC	CTC	AAG	AGG	AAG	CGA	ATT	CTG	CAG	TCG	ACG	GTA	CCG	CGG	GCC	CGG	1824
•	Ser	Leu	Lys	Arg	Lys	Arg	Ile	Leu	Gln	Ser	Thr	Val	Pro	Arg	Ala	Arg	
50			595					600					605				
										_						-	
					GCC												1872
	Asp		Pro	vaı	Ala	Thr		val	Ser	гàг	GLY		Glu	Leu	Pne	Tnr	
55		610					615					620					
55	GGG	GTG	GTG	כככ	ATC	СТС	GTC	GAG	רידוני	GAC	GGC	GAC	ርጥአ	חממ	GGC	CAC	1920
		-10	-10			-10	010	CAG	C10	OAC		U.A.C	~ 147				

	Gly 625	Val	Val	Pro	Ile	Leu 630	Val	Glu	Leu	Asp	Gly 635	Asp	Val	Asn	Gly	His 640	
5				GTG Val													1968
10				AAG Lys 660													2016
				GTG Val					TAC				Cys	TTC			2064
15		Pro	GAC	CAC His			Gln	CAC									2112
20				GTC Val													2160
25	705 TAC	AAG	ACC	CGC Arg	GCC	710 GAG	GTG	AAG	TTC	GAG	715 GGC	GAC	ACC	CTG	GTG	720 AAC	220.8
25	CGC	ATC	GAG	CTG	725 AAG	GGC	ATC	GAC	TTC	730 AAG	GAG	GAC	GGC	AAC	735 ATC	CTG	2256
30				Leu 740 CTG					745			•		750			2204
35				Leu													2304
				CAG Gln													2352
40				GAC Asp													2400
45				GGC Gly													2448
50				TCC Ser 820													2496
			Leu	CTG Leu				Thr	GCC				Thr				2544
55	GAC	GAG	835 CTG	TAC	AAG	TAA		840					845				2562

PCT/DK98/00145 WO 98/45704

224

Asp Glu Leu Tyr Lys 850

(2) INFORMATION FOR SEQ ID NO:119: 5

- (i) SEQUENCE CHARACTERISTICS:
  - (A) LENGTH: 853 amino acids
  - (B) TYPE: amino acid
  - (C) STRANDEDNESS: single
  - (D) TOPOLOGY: linear
- (ii) MOLECULE TYPE: protein
- (v) FRAGMENT TYPE: internal

15

10

(xi) SEQUENCE DESCRIPTION: SEQ ID NO:119:

Met Leu Ser Arg Gly Trp Phe His Arg Asp Leu Ser Gly Leu Asp Ala Glu Thr Leu Leu Lys Gly Arg Gly Val His Gly Ser Phe Leu Ala Arg 20 Pro Ser Arg Lys Asn Gln Gly Asp Phe Ser Leu Ser Val Arg Val Gly 40 Asp Gln Val Thr His Ile Arg Ile Gln Asn Ser Gly Asp Phe Tyr Asp 25 Leu Tyr Gly Gly Glu Lys Phe Ala Thr Leu Thr Glu Leu Val Glu Tyr 70 Tyr Thr Gln Gln Gln Gly Val Leu Gln Asp Arg Asp Gly Thr Ile Ile His Leu Lys Tyr Pro Leu Asn Cys Ser Asp Pro Thr Ser Glu Arg Trp 30 105 Tyr His Gly His Met Ser Gly Gly Gln Ala Glu Thr Leu Leu Gln Ala 120 Lys Gly Glu Pro Trp Thr Phe Leu Val Arg Glu Ser Leu Ser Gln Pro 35 135 Gly Asp Phe Val Leu Ser Val Leu Ser Asp Gln Pro Lys Ala Gly Pro 150 Gly Ser Pro Leu Arg Val Thr His Ile Lys Val Met Cys Glu Gly Gly 170 40 Arg Tyr Thr Val Gly Gly Leu Glu Thr Phe Asp Ser Leu Thr Asp Leu 185 180 Val Glu His Phe Lys Lys Thr Gly Ile Glu Glu Ala Ser Gly Ala Phe 200 Val Tyr Leu Arg Gln Pro Tyr Tyr Ala Thr Arg Val Asn Ala Ala Asp 45 215 Ile Glu Asn Arg Val Leu Glu Leu Asn Lys Lys Gln Glu Ser Glu Asp 230 Thr Ala Lys Ala Gly Phe Trp Glu Glu Phe Glu Ser Leu Gln Lys Gln 245 250 Glu Val Lys Asn Leu His Gln Arg Leu Glu Gly Gln Arg Pro Glu Asn 50 265 Lys Gly Lys Asn Arg Tyr Lys Asn Ile Leu Pro Phe Asp His Ser Arg 280 Val Ile Leu Gln Gly Arg Asp Ser Asn Ile Pro Gly Ser Asp Tyr Ile 55 295 Asn Ala Asn Tyr Ile Lys Asn Gln Leu Leu Gly Pro Asp Glu Asn Ala

	305					310					315					320
	Lys	Thr	Tyr	Ile	Ala 325	Ser	Gln	Gly	Cys	Leu 330	Glu	Ala	Thr	Val	Asn 335	Asp
5	Phe	Trp	Gln	Met 340	Ala	Trp	Gln	Glu	Asn 345	Ser	Arg	Val	Ile	Val 350	Met	Thr
	Thr	Arg	Glu 355	Val	Glu	Lys	Gly	Arg 360	Asn	Lys	Cys	Val	Pro 365	Tyr	Trp	Pro
		370	Gly			_	375		_		_	380				-
10	385		His	_		390		_	-		395					400
i			Asp		405	_			_	410		_		_	415	_
15			Trp	420		,			425					430		
			Leu 435	_				440	_				445			
	•	450	Ile				455		•	-		460	_		_	
20	465		Val		_	470					475			_	_	480
	-		Asp		485			_		490				•	495	
25	_		Gly	500					505		_	_		510		•
			Ala 515					520					<b>52</b> 5			
20		530	Gln				.535					540				
30	545		Met	_		550			-		555					560
		_	Glu Val		565	•				570			•		575	
35		_	Lys	580					585	_	_			590		
			595 Pro					600	•				605			
40	-	610	Val			•	615			-	_	620				
70	625		Ser			630				_	635					640
	•		Leu		645			_		650					655	
45			Leu	660			-		665	_				670		
			675 Asp					680			•		685			
50	_	690					695					700				
50	705		Thr			710					715					720
	•	_	Glu	_	725		•	-		730	-	_			735	
55			Lvs	740					745					750		
	171 1	n i ×	TIV ~	ᆚᄃᄓ		1 V I	A Sin	ivr	A 25 (1)	. oer	пты	0011	va!	T A T		

			755					760					765					
•	Ala	Asp 770		Gln	Lys	Asn	Gly 775	Ile	Lys	Val	Asn	Phe 780	Lys	Ile	Arg	His		
5	Asn 785	Ile	Glu	qaA	Gly	Ser 790	Val	Gln	Leu	Ala	Asp 795	His	Tyr	Gln	Gln	Asn 800		
	Thr	Pro	Ile	Gly	Asp 805	Gly	Pro	Val	Leu	Leu 810	Pro	Asp	Asn	His	Tyr 815			
	Ser	Thr	Gln	Ser 820		Leu	Ser	Lys	Asp 825			Glu	Lys	Arg 830		His		
10	Met	Val	Leu 835	Leu	Glu	Phe	Val	Thr 840		Ala	Gly	Ile	Thr 845		Gly	Met	•	
	Asp	Glu 850	Leu	Tyr	Lys			010			÷		045				•	
15			٠	) INI	FODM:	ተር ጉጥ ል	J FOI	9 CF(	n TĤ	NO.	320.					•		
.0				EQUE!						NO:	120:						•	
		(.	(A)	LENG	GTH:	2994	a bas	зе ра										
20			(C)	TYPI STR	ANDE	ONES	3: si	ingle	e									
				TOPO										•.				
				MOLE( FEAT		TYPI	E: cI	ANC.										
25			(B)	) NAI	CATIO	ON: 3	L2	2991	equei	nce								
				) OTI														
30				SEQUI														
				AAG Lys													4.8	3
35	- 1				5					10					15			
				GAC Asp													96	
				20					25					30				
40				GGC Gly													144	<b>!</b>
			35					40					45					
45				GGC Gly													192	?
		50					55					60						
				GGC Gly													240	)
50	65		-			70	•			- 3	75		<b>F</b>	- <del>-</del>	·- <del>-</del>	80		
				TTC Phe													288	3
55					85	-,-				90	<u></u>	Cry	-1-	141	95	u		
- <del>-</del>	CGC	ACC	ATC	TTC	TTC	AAG	GAC	GAC	GGC	AAC	TAC	AAG	ACC	CGC	GCC	GAG	336	
																		226

	Arg	Thr	Ile	Phe 100	Phe	Lys	Asp	Asp	Gly 105	Asn	Tyr	Lys	Thr	Arg 110	Ala	Glu		
5												ATC Ile					384	1
10	•											CAC His 140					433	2
15												GAC Asp					480	<b>.</b>
												ATC Ile					52	В
20												CCC Pro				_	57	5
25												ACC Thr					624	4
30												GTC Val 220					67:	2
35				_	_							GAG Glu					72	0
55												ACC Thr					76	8
40 .												GAG Glu					81	6
45												TAC Tyr					86	4
50												CTA Leu 300				_	91	2
<b>55</b>												ATT Ile					96	0
55	AAC	CAT	GCC	AAT	GTT	GTA	AAG	GCC	TGT	GAT	GTT	CCT	GAA	GAA	TTG	TAA	100	8

																	•
	Asn	His	Ala	Asn	Val 325	Val	Lys	Ala	Cys	Asp 330	Val	Pro	Glu	Glu	Leu 335	Asn	
5				CAT His								-					1056
10			Leu	CGA Arg									Cys	TGT			1104
				CAG Gln			Ser	ATT									1152
15				CAT													1200
	385			His		390					395	, -				400	
20				CTT Leu													1248
<b>25</b> .				TAT Tyr 420													1296
30				ACA Thr								Leu					1344
35				GCC Ala													1392
33				GCT Ala													1440
40																GCA Ala	1488
45																CAA Gln	1536
50																CTA Leu	1584
																GAC Asp	1632
55	CTT	ACT	TTG	AAG	CAG	CCA	AGA	TGT	TTT	GŢA	TTA	ATG	GAT	CAC	ATT	TTG	1680

WO 98/45704 PCT/DK98/00145

	Leu 545	Thr	Leu	Lys	Gln	Pro 550	Arg	Cys	Phe	Val	Leu 555	Met	Asp	His	Ile	Leu 560	
5		TTG Leu															1728
10		TTT Phe			Pro												1776
45		GAG Glu															1824
15		ACA Thr 610															1872
20		GAT Asp															1920
25		AGT Ser															1968
30		TGT Cys															2016
		CAG Gln															2064
35		AAA Lys 690												_	_		2112
40		AGT Ser															2160
45		ATC Ile															2208
50		AGC Ser															2256
		ATA Ile															2304
55	AAG	GCC	ATC	CAC	TAT	GCT	GAG	GTT	GGT	GTC	ATT	GGA	TAC	CTG	GAG	GAT	2352

	Lys	Ala 770	Ile	His	Tyr	Ala	Glu 775	Val	Gly	Val	Ile	Gly 780	Tyr	Leu	Glu	Asp		
5				TCT Ser							_		_				2400	
10				CGT Arg													2448	
4-5				TAT Tyr 820													2496	
15				ACA Thr													2544	
20			Arg	GTG Val													2592	
25				CAG Gln													2640	
30				ATC Ile													2688	
				AAA Lys 900													2736	
35				CGC Arg													2784	
40				TCA Ser													2832	
45				TGT Cys			Thr					Glu					2880	
50				GAA Glu							His					Ile	2928	
										Ser					Asp	TGG	2976	
55	AGT	TGG	TTA	ACA	GAA	TGA							٠.				2994	230

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Ser Trp Leu Thr Glu
995
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5 (2) INFORMATION FOR SEQ ID NO:121: (i) SEQUENCE CHARACTERISTICS: (A) LENGTH: 997 amino acids (B) TYPE: amino acid 10 (C) STRANDEDNESS: single (D) TOPOLOGY: linear (ii) MOLECULE TYPE: protein (v) FRAGMENT TYPE: internal 15 (xi) SEQUENCE DESCRIPTION: SEQ ID NO:121: Met Val Ser Lys Gly Glu Glu Leu Phe Thr Gly Val Val Pro Ile Leu 10 20 Val Glu Leu Asp Gly Asp Val Asn Gly His Lys Phe Ser Val Ser Gly .20 25 Glu Gly Glu Gly Asp Ala Thr Tyr Gly Lys Leu Thr Leu Lys Phe Ile Cys Thr Thr Gly Lys Leu Pro Val Pro Trp Pro Thr Leu Val Thr Thr 25 Leu Thr Tyr Gly Val Gln Cys Phe Ser Arg Tyr Pro Asp His Met Lys 70 Gln His Asp Phe Phe Lys Ser Ala Met Pro Glu Gly Tyr Val Gln Glu 90 30 Arg Thr Ile Phe Phe Lys Asp Asp Gly Asn Tyr Lys Thr Arg Ala Glu 105 100 Val Lys Phe Glu Gly Asp Thr Leu Val Asn Arg Ile Glu Leu Lys Gly 120 Ile Asp Phe Lys Glu Asp Gly Asn Ile Leu Gly His Lys Leu Glu Tyr 35 135 Asn Tyr Asn Ser His Asn Val Tyr Ile Met Ala Asp Lys Gln Lys Asn 150 155 Gly Ile Lys Val Asn Phe Lys Ile Arg His Asn Ile Glu Asp Gly Ser 170 40 Val Gln Leu Ala Asp His Tyr Gln Gln Asn Thr Pro Ile Gly Asp Gly 185 Pro Val Leu Leu Pro Asp Asn His Tyr Leu Ser Thr Gln Ser Ala Leu 200 Ser Lys Asp Pro Asn Glu Lys Arg Asp His Met Val Leu Leu Glu Phe 45 215 Val Thr Ala Ala Gly Ile Thr Leu Gly Met Asp Glu Leu Tyr Lys Ser 230 235 Gly Leu Arg Ser Arg Ala Gln Ala Ser Asn Ser Thr Met Glu Arg Pro 245 250 50 Pro Gly Leu Arg Pro Gly Ala Gly Gly Pro Trp Glu Met Arg Glu Arg 265 Leu Gly Thr Gly Gly Phe Gly Asn Val Cys Leu Tyr Gln His Arg Glu

275 280 285 Leu Asp Leu Lys Ile Ala Ile Lys Ser Cys Arg Leu Glu Leu Ser Thr

Lys Asn Arg Glu Arg Trp Cys His Glu Ile Gln Ile Met Lys Lys Leu

	305					310					315					320
•					325					330			Glu		335	
5				340					345				Tyr	350		
	_	_	355					360					Cys 365			
•	Lys	Glu 370	Ser	Gln	Ile	Leu	Ser 375	Leu	Leu	Ser	Asp	Ile 380	Gly	Ser	Gly	Ile
10	385	-				390					395	_	Leu			400
	Asn	Ile	Val	Leu	Gln 405	Asp	Val	Gly	Gly	Lys 410	Ile	Ile	His	Lys	Ile 415	Ile
15	qaA	Leu	Gly	Tyr 420	Ala	Lys	Asp	Val	Asp 425	Gln	Gly	Ser	Leu	Cys 430	Thr	Ser
	Phe	Val	Gly 435		Leu	Gln	Tyr	Leu 440	Ala	Pro	Glu	Leu	Phe 445	Glu	Asn	Lys
	Pro	Tyr 450	Thr	Ala	Thr	Val		Tyr	_	Ser	Phe	Gly 460	Thr	Met	Val	Phe
20	465	-				470					475		Leu			480
•					485				_	490			Суѕ	•	495	
25	•			500					505				His	510		
			515					520					Glu 525			
		530				_	535				_	540	Gly			
30	545					550					555		Asp			560
					565					570			Ala		575	
35				580					585				Leu	590		
			595					600					Glu 605			
		610					615					620				
40	625	_				630		_			635		Tyr			640
	•		-		645	-				650			Arg		655	
45				660					665				Gln	670		
•			675					680					Tyr 685			
		690				•	695					700				
50	705					710					715		Met			720
	Leu	Ile	Ser	Ala	Ser 725	Gln	Gln	Leu	Lys	Ala 730	Lys	Leu	Glu	Phe	Phe 735	
55	_			740					745		•		Gln	750		
	Gly	Ile	Ser	Ser	Glu	Lys	Met	Leu	Lys	Ala	Trp	Lys	Glu	Met	Glu	Gli

			755					760					765			•	·
	Lys	Ala 770	Ile	His	Tyr	Ala	Glu 775	Val	Gly	Val	Ile	Gly 780	Tyr	Leu	Glu	Asp	
5		Ile	Met	Ser	Leu	His 790	Ala	Glu	Ile	Met	Gly 795	Leu	Gln	Lys	Ser	Pro 800	
5	785 Tyr	Gly	Arg	Arg	Gln 805		Asp	Leu	Met	Glu 810		Leu	Glu	Gln	Arg 815		
	Ile	qaA	Leu	Tyr 820		Gln	Leu	Lys	His 825		Pro	Ser	Asp	His 830		Tyr	
10	Ser	Asp	Ser 835		Glu	Met	Val	Lys 840		Ile	Val	His	Thr 845		Gln	Ser	
		Asp 850	Arg	Val	Leu	Lys	Glu 855		Phe ·	Gly	His	Leu 860		Lys	Leu	Leu	
15			Lys	Gln	Lys	Ile 870		Asp	Leu	Leu	Pro 875		Val	Glu	Val	Ala 880	
		Ser	Asn		Lys 885		Ala	Asp	Asn	Thr 890		Met	Phe	Met	Gln 895		
	Lys	Arg	Gln			Ile	Trp	His	Leu 905		Lys	Ile	Ala	Cys 910		Gln	
20	Ser	Ser	Ala 915		Ser	Leu	Val	Gly 920		Ser	Leu	Glu	Gly 925		Val	Thr	
	Pro	Gln 930	Thr	Ser	Ala	Trp	Leu 935		Pro	Thr	Ser	Ala 940	-	His	Asp	His	
25	Ser 945		Ser	Cys	Val	Val 950		Pro	Gln	Asp	Gly 955	Glu	Thr	Ser	Ala	Gln 960	
		Ile	Glu	Glu	Asn 965	Leu	Asn	Cys	Leu	Gly 970	His	Leu	Ser	Thr	Ile 975	Ile	
	His	Glu	Ala	Asn 980	Glu	Glu	Gln		Asn 985		Met	Met	Asn	Leu 990	Asp	Trp	
30	Ser	Trp	Leu 995	Thr	Glu				•	•							
			(2)	IN:	FORM	ATIO	N FO	R SE	Q ID	NO:	122:						
35		(:	i) SI														
			(B)	TYP	E: n	299 ucle	ic a	cid									
						DNES: Y: 1		-	е								
40			ii) N			TYP	E: c	DNA									
•		(.	ix) 1														
45			(B)	) LO	CATI	EY: ON: INFO	1	2988	eque	nce							
		(:	xi) :	SEQU	ENCE	DES	CRIP	TION	: SE	Q ID	NO:	122:					
50																GAG Glu	48
55																TAC Tyr	96

5	CAT His										144
5	 CTA Leu 50										192
10	 AAG Lys								_		240
15	 GAA Glu							_		_	288
20	 TGT Cys										336
25	TGT Cys									_	384
	 TCT Ser 130										432
30	Lys Lys										480
35	AAA Lys										528
40	TGT Cys										576 ·
45	GAG Glu									GGG Gly	624
	ATG Met 210						Phe				672
50	CAG Gln										720
<b>55</b>						Glu				AGC Ser	768

GAA AAC TGG CTA CAG TTG ATG TTG AAT TGG GAC CCT CAG CAG AGA GGA Glu Asn Trp Leu Gln Leu Met Leu Asn Trp Asp Pro Gln Gln Arg Gly 275  10  GGA CCT GTT GAC CTT ACT TTG AAG CAG CCA AGA TGT TTT GTA TTA ATG Gly Pro Val Asp Leu Thr Leu Lys Gln Pro Arg Cys Phe Val Leu Met 290  GAT CAC ATT TTG AAT TTG AAG ATA GTA CAC ATC CTA AAT ATG ACT TCT Asp His Ile Leu Asn Leu Lys Ile Val His Ile Leu Asn Met Thr Ser 305  GCA AAG ATA ATA ATA GTA CAC CTT CAT CAN ACT CTA CAT TCA 320			TTA Leu															816
Glu Asn Trp Leu Gln Leu Met Leu Asn Trp Asp Pro Gln Gln Arg Gly 285  10 GGA CCT GTT GAC CTT ACT TTG AAG CAG CCA AGA TGT TTT GTA TTA ATG Gly Pro Val Asp Leu Thr Leu Lys Gln Pro Arg Cys Phe Val Leu Met 290  GAT CAC ATT TTG AAT TTG AAG ATA GTA CAC ATC CTA AAT ATG ACT TCT Asp His Ile Leu Asn Leu Lys Ile Val His Ile Leu Asn Met Thr Ser 305  310  912  960	5																	
275  280  285  10  GGA CCT GTT GAC CTT ACT TTG AAG CAG CCA AGA TGT TTT GTA TTA ATG Gly Pro Val Asp Leu Thr Leu Lys Gln Pro Arg Cys Phe Val Leu Met 290  GAT CAC ATT TTG AAT TTG AAG ATA GTA CAC ATC CTA AAT ATG ACT TCT Asp His Ile Leu Asn Leu Lys Ile Val His Ile Leu Asn Met Thr Ser 305  310  285  912  960  960																		864
Gly Pro Val Asp Leu Thr Leu Lys Gln Pro Arg Cys Phe Val Leu Met 290 295 300  GAT CAC ATT TTG AAT TTG AAG ATA GTA CAC ATC CTA AAT ATG ACT TCT 450 Asp His Ile Leu Asn Leu Lys Ile Val His Ile Leu Asn Met Thr Ser 305 310 315 320		GIU	USII		Deu	GIII	LCU	Nec		ASII	пр	wah	PIO		GIII	ALG	GIY	
290 295 300  GAT CAC ATT TTG AAT TTG AAG ATA GTA CAC ATC CTA AAT ATG ACT TCT 960  15 Asp His Ile Leu Asn Leu Lys Ile Val His Ile Leu Asn Met Thr Ser 305 310 315 320	10																	912
15 Asp His Ile Leu Asn Leu Lys Ile Val His Ile Leu Asn Met Thr Ser 305 310 315 320		Gly		Val	Asp	Leu	Thr		Lys	Gln	Pro	Arg		Phe	Val	Leu	Met	
305 310 315 320		GAT	CAC	ATT	TTG	AAT	TTG	AAG	ATA	GTA	CAC	ATC	CTA	AAT	ATG	ACT	TCT	960
CCN NAC ATA ATT TCT TTT CTC TTN CCN CCT CAT CAN CAN ACT CTT CAT CON	15		His	Ile	Leu	Asn		Lys	Île	Val	His		Leu	Asn	Met	Thr		
GCA AAG ATA ATT TCT TTT CTG TTA CCA CCT GAT GAA AGT CTT CAT TCA 1008		GCA	AAG	ATA	ATT	TCT	TTT	CTG	TTA	CCA	CCT	GAT	GAA	AGT	CTT	CAT	TCA	1008
Ala Lys Ile Ile Ser Phe Leu Leu Pro Pro Asp Glu Ser Leu His Ser		Ala	Lys	Ile	Ile		Phe	Leu	Leu	Pro		Asp	Glu	Ser	Leu		Ser	
20 325 330 335	20					325					330					335		
CTA CAG TCT CGT ATT GAG CGT GAA ACT GGA ATA AAT ACT GGT TCT CAA 1056		CTA	CAG	TCT	CGT	ATT	GAG	CGT	GAA	ACT	GGA	ATA	AAT	ACT	GGT	TCT	CAA	1056
Leu Gln Ser Arg Ile Glu Arg Glu Thr Gly Ile Asn Thr Gly Ser Gln		Leu	Gln	Ser		Ile	Glu	Arg	Glu	Thr	Gly	Ile	Asn	Thr	Gly	Ser	Gln	
340 345 350 25	25				340					345					350			
GAA CTT CTT TCA GAG ACA GGA ATT TCT CTG GAT CCT CGG AAA CCA GCC 1104	20	GAA	CTT	CTT	TCA	GAG	ACA	GGA	ATT	TCT	CTG	GAT	CCT	CGG	AAA	CCA	GCC	1104
Glu Leu Leu Ser Glu Thr Gly Ile Ser Leu Asp Pro Arg Lys Pro Ala		Glu	Leu		Ser	Glu	Thr	Gly	Ile	Ser	Leu	Asp	Pro	Arg	Lys	Pro	Ala	
355 360 365				355					360					365				
30 TCT CAA TGT GTT CTA GAT GGA GTT AGA GGC TGT GAT AGC TAT ATG GTT 1152	30	TCT	CAA	TGT	GTT	CTA	GAT	GGA	GTT	AGA	GGC	TGT	GAT	AGC	TAT	ATG	GTT	1152
Ser Gln Cys Val Leu Asp Gly Val Arg Gly Cys Asp Ser Tyr Met Val		Ser	Gln	Сув	Val	Leu	Asp	Gly	Val	Arg	Gly	Cys	Asp	Ser	Tyr	Met	Val	
370 375 380			370					375	•				380					
TAT TTG TTT GAT AAA AGT AAA ACT GTA TAT GAA GGG CCA TTT GCT TCC 1200		TAT	TTG	TTT	GAT	AAA	AGT	AAA	ACT	GTA	TAT	GAA	GGG	CCA	TTT	GCT	TCC	1200
35 Tyr Leu Phe Asp Lys Ser Lys Thr Val Tyr Glu Gly Pro Phe Ala Ser	35																	
385 390 395 400		385					390					395					400	
AGA AGT TTA TCT GAT TGT GTA AAT TAT ATT GTA CAG GAC AGC AAA ATA 1248		AGA	AGT	TTA	TCT	GAT	TGT	GTA	AAT	TAT	ATT	GTA	CAG	GAC	AGC	AAA	ATA	1248
Arg Ser Leu Ser Asp Cys Val Asn Tyr Ile Val Gln Asp Ser Lys Ile																		
40 405 410 415	40					405					410					415		
CAG CTT CCA ATT ATA CAG CTG CGT AAA GTG TGG GCT GAA GCA GTG CAC 1296		CAG	CTT	CCA	ATT	ATA	CAG	CTG	CGT	AAA	GTG	TGG	GCT	GAA	GCA	GTG	CAC	1296
Gln Leu Pro Ile Ile Gln Leu Arg Lys Val Trp Ala Glu Ala Val His																		
420 425 430	45				420					425		٠			430			
TAT GTG TCT GGA CTA AAA GAA GAC TAT AGC AGG CTC TTT CAG GGA CAA 1344	45	тат	GTG	тст	GGA	СТА	444	GAD	GAC	тат	AGC	AGG	כדכ	արար	CAG	GGA	CAA	1344
Tyr Val Ser Gly Leu Lys Glu Asp Tyr Ser Arg Leu Phe Gln Gly Gln																		2011
435 440 445				435					440			_		445				
50 AGG GCA GCA ATG TTA AGT CTT CTT AGA TAT AAT GCT AAC TTA ACA AAA 1392	50	<b>V</b> GG	GCA	GCA	ΔጥC	ጥጥል	ልርም	سس	Curur	עיטע	ጥለጥ	ידי אול	GCT	ልአሮ	ጥጥል	ልሮል	444	1392
Arg Ala Ala Met Leu Ser Leu Leu Arg Tyr Asn Ala Asn Leu Thr Lys	00																	1332
450 455 460											•						-	
מער מאר מער מער מער מער מער מער מער מער מער מע		איזירי	አአር	מ מ	Σ ריπי	تابلىك	מינת	ጥርን	CON	Tr.C.»	(1 N N	(1 N N	CTTC	<b>ת</b> ת ת	C Cm	תתת	שיחיכי	1440
ATG AAG AAC ACT TTG ATC TCA GCA TCA CAA CAA CTG AAA GCT AAA TTG 1440  55 Met Lys Asn Thr Leu Ile Ser Ala Ser Gln Gln Leu Lys Ala Lys Leu	55																	1440
465 470 475 480														4		4		

. 5							_	_							AGC Ser 495		1488
Ü									•						TGG Trp		1536
10															ATT Ile		1584
15															GGG Gly		1632
20															TCT Ser		1680
25	Glu	Gln	Arg	Ala	11e 565	Asp	Leu	Tyr	Lys	Gln 570	Leu	Lys	His	Arg	Pro 575	Ser	1728
	Asp	His	Ser	Tyr 580	Ser	Asp	Ser	Thr	Glu 585	Met	Val	Lys	Ile	Ile 590	GTG Val	His	1776
, 30	Thr	Val	Gln 595	Ser	Gln	Asp	Arg	Val 600	Leu	Lys	Glu	Leu	Phe 605	Gly	CAT	Leu	1824
35	Ser	Lys 610	Leu	Leu	Gly	Cys	Lys 615	Gln	Lys	Ile	Ile	Asp 620	Leu	Leu	Pro	Lys	1872
40	Val 625	Glu	Val	Ala	Leu	Ser 630	Asn	Ile	Lys	Glu	Ala 635	Asp	Asn	Thr	GTC Val	Met 640	1920
45	Phe	Met	Gln	Gly	Lys 645	Arg	Gln	Lys	Glu	Ile 650	Trp	His	Leu	Leu	AAA Lys 655	Ile	1968
													•		CTA Leu		2016
50															TCA Ser		2064
55															GGG		2112

5														GGC Gly			2160
														AGT Ser			2208
10	Asn	Leu	Asp	Trp 740	Ser	Trp	Leu	Thr	Glu 745	Trp	Val	Pro	Arg	GCC Ala 750	Arg	Asp	2256
15												Glu		TTC		GGG Gly	2304
20	Val	Val 770	Pro	Ile	Leu	Val	Glu 775	Leu	Asp	Gly	Asp	Val 780	Asn	GGC	His	Lys	2352
25	Phe 785	Ser	Val	Ser	Gly	Glu 790	Gly	Glu	Gly	Asp	Ala 795	Thr	Tyr	GGC Gly	ГÀЗ	Leu 800	2400
														CCC Pro			2448
30														AGC Ser 830			2496
35				•										ATG Met			2544
40								Ile						GGC Gly			2592
45														GTG Val			2640
														ATC Ile			2688
50														ATC Ile 910			2736
55														CGC Arg			2784

5		GAG Glu 930															2832
		ATC Ile															2880
10		CAG Gln															2928
15		CTG Leu															2976
20		CTG Leu			TAA			x +				•			•		2991
			(2)	INI	FORM	OITA	1 FOI	R SE	Q ID	NO:	123:						
25		<b>( )</b>	(A) (B) (C)	LENG TYPI STRA	ETH: E: ar ANDEI	CHARA 996 mino ONESS	amin acio 3: s:	no ao i ingle	cids								·
30		(7	Li) I	MOLEC RAGMI	CULE ENT '	TYPI IYPE DES	E: p:	rote: terna	al	o ID	NO:	123:					
35		Glu			Pro					Gly			Gly	Pro		Glu	
	1 Met	Arg	Glu	Arg 20	5 Leu	Gly	Thr	Gly	Gly 25	10 Phe	Gly	Asn	Val	Cys	15 Leu	Tyr	
40	Gln	His	Arg 35		Leu	Asp	Leu	Lys 40		Ala	Ile	Lys	Ser 45		Arg	Leu	
		50				,	55					60				Ile	
		Lys	Lys	Leu	Asn		Ala	Asn	Val	Val	_	Ala	Cys	Asp	Val	Pro	
45	65 Glu	Glu	Leu		Ile 85	70 Leu	Ile	His	Asp	Val 90	75 Pro	Leu	Leu	Ala	Met 95	80 Glu	
	Tyr	Cys	Ser			Asp	Leu	Arg	Lys 105	Leu	Leu	Asn	Lys	Pro	Glu	Asn	
50	Cys	Cys	Gly 115		Lys	Glu	Ser	Gln 120	Ile		Ser	Leu	Leu 125	Ser		Ile	
	Gly	Ser 130		Ile	Arg	Tyr	Leu 135	His		Asn	Lys	Ile 140	Ile		Arg	Asp	
	Leu		Pro	Glu	Asn	Ile	Val	Leu	Gln	Asp	Val	Gly	Gly	Lys	Ile	lle	
55	145				_	150					155		_	<b>.</b>	<b></b> -	160	
	His	Lys	Ile	Ile	Asp	Leu	Gly	Tyr	Ala	Lys	Asp	Val	Asp	Gln	Gly	Ser	

					165					170					175	
	Leu	Cys	Thr			Val	Gly	Thr			Tyr	Leu	Ala		Glu	Leu
	Dhe	Glu	Δen	180	Pro	Tvr	Thr	Ala	185 Thr	Val	Asp	Tvr	Trp	190 Ser	Phe	Glv
5	FIIC	Giu	195	_,	110	-7-		200		***		-1-	205			1
	Thr	Met 210	Val	Phe	Glu	Cys	Ile 215	Ala	Gly	Tyr	Arg	Pro 220	Phe	Leu	His	His
	Leu 225		Pro	Phe	Thr	Trp 230	His	Glu	Lys	Ile	Lys 235	Lys	Lys	Asp	Pro	Lys 240
10		Ile	Phe	Ala	Cys 245		Glu	Met	Ser	Gly 250		Val	Arg	Phe	Ser 255	Ser
	His	Leu	Pro	Gln 260		Asn	Ser	Leu	Cys 265		Leu	Ile	Val	Glu 270	Pro	Met
15	Glu	Asn	Trp 275		Gln	Leu	Met	Leu 280		Trp	Asp	Pro	Gln 285	Gln	Arg	Gly
10	Gly	Pro 290	Val	Asp	Leu	Thr	Leu 295		Gln	Pro	Arg	Cys 300	Phe	Val	Leu	Met
	Asp			Leu	Asn	Leu 310	Lys	Ile	Val	His	Ile 315	Leu	Asn	Met	Thr	Ser 320
20		Lys	Ile	Ile	Ser 325	Phe	Leu	Leu	Pro	Pro 330	Asp	Glu	Ser	Leu	His 335	Ser
	Leu	Gln	Ser	Arg 340	lle	Glu	Arg	Glu	Thr 345		Ile	Asn	Thr	Gly 350	Ser	Gln
25	Glu	Leu	Leu 355	Ser	Glu	Thr	Gly	Ile 360	Ser	Leu	Asp	Pro	Arg 365	Lys	Pro	Ala
	Ser	Gln 370	Cys	Val	Leu	Asp	Gly 375	Val	Arg	Gly	Cys	Asp 380	Ser	Tyr	Met	Val
	385					390					395				Ala	400
30	_				405					410					Lys 415	
				420					425					430	Val	
35	_		435					440					445		Gly	
		450					455					460			Thr	
	465	-				470				•	475				Lys	480
40					485					490					495	Glu
		•	•	500					505					510		Lys
45			515					520					525			Gly -
	_	530					535					540				Leu
	545	_				550			•		555					Leu 560
50					565				•	570					575	
				580		•			585					590		His
55			595					600					605	i		Leu
	Ser	Lys	Leu	Leu	Gly	Cys	Lys	Gln	Lys	Ile	lle	Asp	Leu	Leu	Pro	Lys

25																	
625			610					615					620				
Phe Met   Gln Gly Lys Arg Gln Lys Glu Ile Trp His Leu Leu Lys Ile   650   655   655   655   655   655   655   655   655   655   655   655   655   655   655   650   650   660   660   660   660   660   660   660   660   665   660   665   660   665   660   665   660   665   665   660   665   665   660   665   665   660   665   665   660   665   665   665   665   665   665   665   660   665   665   665   665   665   665   665   665   665   665   665   665   665   665   665   665   665   665   665   665   665   665   665   665   665   665   665   665   665   665   665   665   665   665   665   665   665   665   665   665   665   665   665   665   665   665   665   665   665   665   665   665   665   665   665   665   665   665   665   665   665   665   665   665   665   665   665   665   665   665   665   665   665   665   665   665   665   665   665   665   665   665   665   665   665   665   665   665   665   665   665   665   665   665   665   665   665   665   665   665   665   665   665   665   665   665   665   665   665   665   665   665   665   665   665   665   665   665   665   665   665   665   665   665   665   665   665   665   665   665   665   665   665   665   665   665   665   665   665   665   665   665   665   665   665   665   665   665   665   665   665   665   665   665   665   665   665   665   665   665   665   665   665   665   665   665   665   665   665   665   665   665   665   665   665   665   665   665   665   665   665   665   665   665   665   665   665   665   665   665   665   665   665   665   665   665   665   665   665   665   665   665   665   665   665   665   665   665   665   665   665   665   665   665   665   665   665   665   665   665   665   665   665   665   665   665   665   665   665   665   665   665   665   665   665   665   665   665   665   665   665   665   665   665   665   665   665   665   665   665   665   665   665   665   665   665   665   665   665   665   665   665   665   665   665   665   665   665   665   665   665   665   665   665   665   665   66		Val	Glu	Val	Ala	Leu	Ser	Asn	Ile	Lys	Glu	Ala	Asp	Asn	Thr	Val	Met
645																	
Ala Cys Thr Gln Ser Ser Ala Arg Ser Leu Val Gly Ser Ser Leu Glu 660 665 665 670 681 682 683 684 685 685 685 685 686 685 686 685 686 687 688 687 688 688 688 688 688 688		Phe	Met	Gln	Gly	Lys	Arg	Gln	Lys	Glu	Ile	Trp	His	Leu	Leu	Lys	Ile
Gly Ala   Val Thr   Pro   Gln   Thr   Ser   Ala   Glo   Ges   Ge	5					645					650					655	
Gly Ala Val Thr		Ala	Cys	Thr	Gln	Ser	Ser	Ala	Arg	Ser	Leu	Val	Gly	Ser	Ser	Leu	Glu
10					660					665					670	,	
10		Gly	Ala	Val	Thr	Pro	Gln	Thr	Ser	Ala	Trp	Leu	Pro	Pro	Thr	Ser	Ala
Thi Ser																	
Thr Ser Ala Gln Met Ile Glu Glu Asn Leu Asn Cys Leu Gly His Leu 705	10	Glu	His	Asp	His	Ser	Leu	Ser	Cys	Val	Val	Thr	Pro	Gln	Asp	Gly	Glu
105																	
Ser   Thr   The   He   He   He   He   The   He   The		Thr	Ser	Ala	Gln	Met	Ile	Glu	Glu	Asn	Leu		Cys	Leu	Gly	His	
15				7							_						
Asn Leu Asp Trp Ser Trp Leu Trp Glu Trp Val Pro Arg Ala Arg Asp 740		Ser	Thr	Ile	Ile		Glu	Ala	Asn	Glu		Gln	Gly	Asn	Ser		Met
Pro   Pro   Val   Ala   The   Met   Val   Ser   Lys   Glu   Glu   Leu   Phe   The   Gly   755   765   765   765   765   765   765   765   765   765   765   765   765   765   765   765   765   765   765   765   765   765   765   765   765   765   765   765   765   765   765   765   765   765   765   765   765   765   765   765   765   765   765   765   765   765   765   765   765   765   765   765   765   765   765   765   765   765   765   765   765   765   765   765   765   765   765   765   765   765   765   765   765   765   765   765   765   765   765   765   765   765   765   765   765   765   765   765   765   765   765   765   765   765   765   765   765   765   765   765   765   765   765   765   765   765   765   765   765   765   765   765   765   765   765   765   765   765   765   765   765   765   765   765   765   765   765   765   765   765   765   765   765   765   765   765   765   765   765   765   765   765   765   765   765   765   765   765   765   765   765   765   765   765   765   765   765   765   765   765   765   765   765   765   765   765   765   765   765   765   765   765   765   765   765   765   765   765   765   765   765   765   765   765   765   765   765   765   765   765   765   765   765   765   765   765   765   765   765   765   765   765   765   765   765   765   765   765   765   765   765   765   765   765   765   765   765   765   765   765   765   765   765   765   765   765   765   765   765   765   765   765   765   765   765   765   765   765   765   765   765   765   765   765   765   765   765   765   765   765   765   765   765   765   765   765   765   765   765   765   765   765   765   765   765   765   765   765   765   765   765   765   765   765   765   765   765   765   765   765   765   765   765   765   765   765   765   765   765   765   765   765   765   765   765   765   765   765   765   765   765   765   765   765   765   765   765   765   765   765   765   765   765   765   765   765   765   765   765   765   765   765   765   765   765   765	15							_					_		_ ,		
Pro		Asn	Leu	Asp		Ser	Trp	Leu	Thr		Trp	Val	Pro	Arg		Arg	Asp
1		_	_	**		m)	<b>M</b> - <b>h</b>	**- 3	G		<b>a</b> 3	a1	~1	T		The	<i>α</i> 1
Nal		Pro	Pro		Ата	Thr	Met	vaı		гуѕ	GIY	GIU	GIU		Pne	TIII	GIY
Pho   Ser   Val   Ser   Ser   Gly   Glu   Gly   Gly   Gly   Ser   Asp   Asp   Asp   Asp   Try   Gly   Lys   Leu   Roy	20	17.5 3	1707		TIO	Tan	Wa 1	Glu		λαη	Gly	Λen	V=1		Glv	ніс	Lve
Phe   Ser   Val   Ser   Gly   Glu   Gly   Glu   Gly   Asp   Ala   Thr   Tyr   Gly   Lys   Leu   785   785   790   790   790   795   795   795   795   795   795   795   795   795   795   795   795   795   795   795   795   795   795   795   795   795   795   795   795   795   795   795   795   795   795   795   795   795   795   795   795   795   795   795   795   795   795   795   795   795   795   795   795   795   795   795   795   795   795   795   795   795   795   795   795   795   795   795   795   795   795   795   795   795   795   795   795   795   795   795   795   795   795   795   795   795   795   795   795   795   795   795   795   795   795   795   795   795   795   795   795   795   795   795   795   795   795   795   795   795   795   795   795   795   795   795   795   795   795   795   795   795   795   795   795   795   795   795   795   795   795   795   795   795   795   795   795   795   795   795   795   795   795   795   795   795   795   795   795   795   795   795   795   795   795   795   795   795   795   795   795   795   795   795   795   795   795   795   795   795   795   795   795   795   795   795   795   795   795   795   795   795   795   795   795   795   795   795   795   795   795   795   795   795   795   795   795   795   795   795   795   795   795   795   795   795   795   795   795   795   795   795   795   795   795   795   795   795   795   795   795   795   795   795   795   795   795   795   795   795   795   795   795   795   795   795   795   795   795   795   795   795   795   795   795   795   795   795   795   795   795   795   795   795   795   795   795   795   795   795   795   795   795   795   795   795   795   795   795   795   795   795   795   795   795   795   795   795   795   795   795   795   795   795   795   795   795   795   795   795   795   795   795   795   795   795   795   795   795   795   795   795   795   795   795   795   795   795   795   795   795   795   795   795   795   795   795   795   795   795   795   795   795   795   795	20	vaı		PIO	116	ьeu	vai		цец	Asp	GIY	Asp		ASII	GLY	1112	Буб
785		Dhe		Val	Ser	Glv	Glu		Glu	Glv	Δsn	Δla		Tvr	Glv	Lvs	Leu
The Leu Lys Phe 11e Cys The The Gly Lys Leu Pro Val Pro Trp Pro 815  The Leu Val The The Leu The The Set The Set Set Set Set Set Set Set Set Set Se			261		DCI	Gry		Cry	Gru	Oly	пор			- / -	<b>-</b>	272	
The   Leu   Val   The   The   Leu   The   The   Leu   The			Leu	Lvs	Phe	Ile		Thr	Thr	Glv	Lvs		Pro	Val	Pro	Trp	
The Leu Val The The Leu The The Seve Th	25			-,-			-1-			1							
Pro   Asp   His   Met   Lys   Gln   His   Asp   Pro   Riv   Ser   Ala   Met   Pro   Glu   Riv		Thr	Leu	Val	Thr	Thr	Leu	Thr	Tyr	Gly	Val	Gln	Cys	Phe	Ser	Arg	Tyr
30									_				_				
30 Gly Tyr Val Gln Glu Arg Thr Ile Phe Phe Lys Asp Asp Gly Asn Tyr 850		Pro	Asp	His	Met	Lys	Gln	His	Asp	Phe	Phe	Lys	Ser	Ala	Met	Pro	Glu
1																	
Lys Thr Arg Ala Glu Val Lys Phe Glu Gly Asp Thr Leu Val Asn Arg 865	30	Gly	Tyr	Val	Gln	Glu	Arg	Thr	Ile	Phe	Phe	Lys	Asp	Asp	Gly	Asn	Tyr
865																	
The Glu Leu Lys Gly Ile Asp Phe Lys Glu Asp Gly Asn Ile Leu Gly 885		Lys	Thr	Arg	Ala	Glu		Lys	Phe	Glu	Gly		Thr	Leu	Val	Asn	
35									_							_	
His Lys Leu Glu Tyr Asn Tyr Asn Ser His Asn Val Tyr Ile Met Ala 900		Ile	Glu	Leu	Lys		Ile	Asp	Phe	Lys			Gly	Asn	He		GIÀ
Asp Lys Gln Lys Asn Gly Ile Lys Val Asn Phe Lys Ile Arg His Asn 915	35			_			_		_	_				<b></b>	71-		77-
Asp Lys Gln Lys Asn Gly Ile Lys Val Asn Phe Lys Ile Arg His Asn 915   1   20   20   20   20   20   20   20		His	Lys	Leu		Tyr	Asn	Tyr	Asn		His	Asn	vaı	Tyr		Met	Ala
40 Ile Glu Asp Gly Ser Val Gln Leu Ala Asp His Tyr Gln Gln Asn Thr 930		3		<b>~1</b>		7	C1	71.	T		700	Dho	Tare	Tle		uie	Aen
40 Ile Glu Asp Gly Ser Val Gln Leu Ala Asp His Tyr Gln Gln Asn Thr 930		Asp	гла		пуѕ	ASI	GIY	TTE		vaı	ASII	Pne	пуѕ		Arg	пть	Maii
930	40	Tla	Clu		Glaz	Cor	Val	Gla		בות	yen	Hie	ጥህጕ		Gln	Asn	Thr
Pro Ile Gly Asp Gly Pro Val Leu Leu Pro Asp Asn His Tyr Leu Ser 945	40	TTE		Asp	Gry	361	vai		Бец	AIG	лар	1112		04,11	0		
945 950 955 960  Thr Gln Ser Ala Leu Ser Lys Asp Pro Asn Glu Lys Arg Asp His Met  45  Val Leu Leu Glu Phe Val Thr Ala Ala Gly Ile Thr Leu Gly Met Asp 980  Glu Leu Tyr Lys 995		Pro		Glv	Asp	Glv	Pro		Leu	Leu	Pro	Asp		His	Tvr	Leu	Ser
Thr Gln Ser Ala Leu Ser Lys Asp Pro Asn Glu Lys Arg Asp His Met 965  Val Leu Leu Glu Phe Val Thr Ala Ala Gly Ile Thr Leu Gly Met Asp 980  Glu Leu Tyr Lys 995				01,											- 2		
965 970 975  Val Leu Leu Glu Phe Val Thr Ala Ala Gly Ile Thr Leu Gly Met Asp 980 985 990  Glu Leu Tyr Lys 995				Ser	Ala	Leu		Lvs	Asp	Pro	Asn		Lys	Arg	Asp	His	Met
Val Leu Leu Glu Phe Val Thr Ala Ala Gly Ile Thr Leu Gly Met Asp 980 985 990 Glu Leu Tyr Lys 995	45	•						•	•				-		_		
980 985 990 Glu Leu Tyr Lys 995		Val	Leu	Leu	Glu	Phe	Val	Thr	Ala	Ala	Gly	Ile	Thr	Leu	Gly	Met	Asp
995											_						
		Glu	Leu	Tyr	Lys												
50				995													
	50																

(2) INFORMATION FOR SEQ ID NO:124:

- (i) SEQUENCE CHARACTERISTICS:
  - (A) LENGTH: 1908 base pairs
  - (B) TYPE: nucleic acid

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(C) STRANDEDNESS: single

(D) TOPOLOGY: line	ear
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## (ii) MOLECULE TYPE: cDNA

(ix) FEATURE:

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(A) NAME/KEY: Coding Sequence
(B) LOCATION: 1...1905
(D) OTHER INFORMATION:

10 (xi) SEQUENCE DESCRIPTION: SEQ ID NO:124: ATG GTG AGC AAG GGC GAG GAG CTG TTC ACC GGG GTG GTG CCC ATC CTG 48 Met Val Ser Lys Gly Glu Glu Leu Phe Thr Gly Val Val Pro Ile Leu 5 15 GTC GAG CTG GAC GGC GAC GTA AAC GGC CAC AAG TTC AGC GTG TCC GGC 96 Val Glu Leu Asp Gly Asp Val Asn Gly His Lys Phe Ser Val Ser Gly 20 20 GAG GGC GAG GGC GAT GCC ACC TAC GGC AAG CTG ACC CTG AAG TTC ATC 144 Glu Gly Glu Gly Asp Ala Thr Tyr Gly Lys Leu Thr Leu Lys Phe Ile TGC ACC ACC GGC AAG CTG CCC GTG CCC TGG CCC ACC CTC GTG ACC ACC Cys Thr Thr Gly Lys Leu Pro Val Pro Trp Pro Thr Leu Val Thr Thr 25 CTG ACC TAC GGC GTG CAG TGC TTC AGC CGC TAC CCC GAC CAC ATG AAG 240 Leu Thr Tyr Gly Val Gln Cys Phe Ser Arg Tyr Pro Asp His Met Lys 30 70 CAG CAC GAC TTC TTC AAG TCC GCC ATG CCC GAA GGC TAC GTC CAG GAG 288 Gln His Asp Phe Phe Lys Ser Ala Met Pro Glu Gly Tyr Val Gln Glu 35 CGC ACC ATC TTC TTC AAG GAC GAC GGC AAC TAC AAG ACC CGC GCC GAG 336 Arg Thr Ile Phe Phe Lys Asp Asp Gly Asn Tyr Lys Thr Arg Ala Glu 100 105 384 40 GTG AAG TTC GAG GGC GAC ACC CTG GTG AAC CGC ATC GAG CTG AAG GGC Val Lys Phe Glu Gly Asp Thr Leu Val Asn Arg Ile Glu Leu Lys Gly 115 120 ATC GAC TTC AAG GAG GAC GGC AAC ATC CTG GGG CAC AAG CTG GAG TAC 432 45 Ile Asp Phe Lys Glu Asp Gly Asn Ile Leu Gly His Lys Leu Glu Tyr 130 135 AAC TAC AAC AGC CAC AAC GTC TAT ATC ATG GCC GAC AAG CAG AAG AAC 480 Asn Tyr Asn Ser His Asn Val Tyr Ile Met Ala Asp Lys Gln Lys Asn 50 145 GGC ATC AAG GTG AAC TTC AAG ATC CGC CAC AAC ATC GAG GAC GGC AGC 528 Gly Ile Lys Val Asn Phe Lys Ile Arg His Asn Ile Glu Asp Gly Ser 165 55

241

GTG CAG CTC GCC GAC CAC TAC CAG CAG AAC ACC CCC ATC GGC GAC GGC

	Val	Gln	Leu	Ala 180	Asp	His	Tyr	Gln	Gln 185	Asn	Thr	Pro	Ile	Gly 190	Asp	Gly		
5														TCC Ser			624	
10														CTG Leu			672	
														TAC Tyr			720	
15														GTC Val			768	
20														CTT Leu 270			816	
25				Lys										CAG Gln			864	
- 30														TTT Phe			912	
														AAC Asn			960	
35														TTC Phe			1008	
40														AGC Ser 350			1056	
45									Met					GAG Glu		•	1104	
50			Gly					Pro					Thr	TGG Trp		GTC Val	1152	
		Asn					Glu					Gln				CAG Gln 400	1200	
55	ccc	GGC	CCG	TCG	GAG	CAC	ATA	GAG	CGC	CGG	GTC	TCC	TAA :	GCA	. GGA	GGC	1248	242

	Pro	Gly	Pro	Ser	Glu 405	His	Ile	Glu	Arg	Arg 410	Val	Ser	Asn	Ala	Gly 415	Gly		
5				CCC Pro 420												CCC Pro	1296	
10				GGT Gly													1344	
15				GCG Ala													1392	
13				GCA Ala													1440	
20				GCT Ala													1488	
25				TCA Ser 500													1536	
30				GGG Gly													1584	
			Lys	GCC Ala													1632	
35				GAG Glu											_		1680	
40				CCC Pro													1728	
45				TCG Ser 580						Thr							1776	
50				Tyr										Leu		GAA Glu	1824	
			Lys					Lys					Ile			GCC Ala	1872	
55	TTC	GTC	CAG	GAG	CTG	AGG	AAG	CGG	GGT	TÇT	ccc	TGA					1908 2	43

Phe Val Gln Glu Leu Arg Lys Arg Gly Ser Pro 625 630 635

5 (2) INFORMATION FOR SEQ ID NO:125:

- (i) SEQUENCE CHARACTERISTICS:
  - (A) LENGTH: 635 amino acids
  - (B) TYPE: amino acid
  - (C) STRANDEDNESS: single
  - (D) TOPOLOGY: linear
- (ii) MOLECULE TYPE: protein
- (v) FRAGMENT TYPE: internal

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(xi) SEQUENCE DESCRIPTION: SEQ ID NO:125:

Met Val Ser Lys Gly Glu Glu Leu Phe Thr Gly Val Val Pro Ile Leu Val Glu Leu Asp Gly Asp Val Asn Gly His Lys Phe Ser Val Ser Gly 20 2.5 Glu Gly Glu Gly Asp Ala Thr Tyr Gly Lys Leu Thr Leu Lys Phe Ile Cys Thr Thr Gly Lys Leu Pro Val Pro Trp Pro Thr Leu Val Thr Thr 25 Leu Thr Tyr Gly Val Gln Cys Phe Ser Arg Tyr Pro Asp His Met Lys Gln His Asp Phe Phe Lys Ser Ala Met Pro Glu Gly Tyr Val Gln Glu 90 Arg Thr Ile Phe Phe Lys Asp Asp Gly Asn Tyr Lys Thr Arg Ala Glu 30 105 Val Lys Phe Glu Gly Asp Thr Leu Val Asn Arg Ile Glu Leu Lys Gly 125 120 Ile Asp Phe Lys Glu Asp Gly Asn Ile Leu Gly His Lys Leu Glu Tyr 135 35 Asn Tyr Asn Ser His Asn Val Tyr Ile Met Ala Asp Lys Gln Lys Asn 150 Gly Ile Lys Val Asn Phe Lys Ile Arg His Asn Ile Glu Asp Gly Ser 170 165 Val Gln Leu Ala Asp His Tyr Gln Gln Asn Thr Pro Ile Gly Asp Gly 40 .185 Pro Val Leu Leu Pro Asp Asn His Tyr Leu Ser Thr Gln Ser Ala Leu 200 Ser Lys Asp Pro Asn Glu Lys Arg Asp His Met Val Leu Leu Glu Phe 45 215 Val Thr Ala Ala Gly Ile Thr Leu Gly Met Asp Glu Leu Tyr Lys Ser 235 230 Gly Leu Arg Ser Arg Ala Gln Ala Ser Met Ser Glu Thr Val Ile Met 250 245 Ser Glu Thr Val Ile Cys Ser Ser Arg Ala Thr Val Met Leu Tyr Asp 50 265 Asp Gly Asn Lys Arg Trp Leu Pro Ala Gly Thr Gly Pro Gln Ala Phe 280 Ser Arg Val Gln Ile Tyr His Asn Pro Thr Ala Asn Ser Phe Arg Val

295

Val Gly Arg Lys Met Gln Pro Asp Gln Gln Val Val Ile Asn Cys Ala

	305					310					315					320
			Arg		325					330					335	
5	-	_	Asp	340					345					350		
	_		Ala 355					360					365			
٠		370	Gly	_			375					380				
10	385		Gly			390					395				•	400
•		_	Pro		405					410					415	
15			Ala	420		•			425					430		
		•	Pro 435					440					445			
		450	Ala				455					460				
20	465		Ala			470		,			475					480
			Ala		485					490					495	
25			Ala	500					505					510		
		_	Gly 515	_	_			520					525			
		530					535		•			540				
30	545		Gln			550					555					560
		_	Arg		565					570					575	
35			Ser	580					585					590		
			Asp 595					600	,				605			
		610		-		٠.	615					620		Ile	Glu	Ala
40	Phe 625		Gln	Glu	Leu	Arg 630	_	Arg	Gly	Ser	635					
			(2	) IN	FORM	ATIO	N FC	R SE	Q ID	NO:	126:				•	
45		(	i) s													
			(B)	TYP	GTH: E: n	ucle	ic a	cid		ł						
					ANDE			_	.e							
50			(ii) (ix)				E: c	:DNA								
55					ME/K			_	_	ence,						
				٠, ٥,,	111TD	TATES	N 1 2 2 2									

## (xi) SEQUENCE DESCRIPTION: SEQ ID NO:126:

5	ATG Met 1	GTG Val	AGC Ser	AAG Lys	GGC Gly 5	GAG Glu	GAG Glu	CTG Leu	TTC Phe	ACC Thr 10	GGG Gly	GTG Val	GTG Val	Pro	ATC Ile 15	CTG Leu	48	
10	GTC Val	GAG Glu	CTG Leu	GAC Asp 20	GGC Gly	GAC Asp	GTA Val	AAC Asn	GGC Gly 25	CAC His	AAG Lys	TTC Phe	AGC Ser	GTG Val 30	TCC Ser	GGC Gly	96	
15	GAG Glu	GGC Gly	GAG Glu 35	GGC Gly	GAT Asp	GCC Ala	ACC Thr	TAC Tyr 40	GGC Gly	AAG Lys	CTG Leu	ACC Thr	CTG Leu 45	AAG Lys	TTC Phe	ATC Ile	144	
10 .	TGC Cys	ACC Thr 50	ACC Thr	GGC Gly	AAG Lys	CTG Leu	CCC Pro 55	GTG Val	CCC Pro	TGG Trp	CCC	ACC Thr 60	CTC Leu	GTG Val	ACC Thr	ACC Thr	192	
20	CTG Leu 65	ACC Thr	TAC Tyr	GGC Gly	GTG Val	CAG Gln 70	TGC Cys	TTC Phe	AGC Ser	CGC Arg	TAC Tyr 75	CCC Pro	GAC Asp	CAC His	ATG Met	AAG Lys 80	240	
25	Gln	His	Asp	Phe	Phe 85	Lys	Ser	Ala	Met	Pro 90	Glu	Gly	Tyr	GTC Val	Gln 95	Glu	288	
30	Arg	Thr	Ile	Phe 100	Phe	Lys	Asp	Asp	Gly 105	Asn	Tyr	Lys	Thr	CGC Arg 110	Ala	Glu	336	
35	Val	Lys	Phe 115	Glu	Gly	Asp	Thr	Leu 120	. Val	Asn	Arg	Ile	Glu 125		Гув	Gly	384	
	Ile	Asp 130	Phe	Lys	Glu	Asp	Gly 135	Asn	Ile	Leu	Gly	His 140	Lys	Leu	Glu	TAC Tyr	432	
40	Asn 145	Туг	Asn	Ser	His	Asn 150	Val	Туг	: Ile	Met	155	Asp	Lys	Gln	Lys	AAC Asn 160	480	
45	Gly	, Ile	E Lys	Val	. Asr 165	n Ph∈	: Буз	: Ile	e Arg	170	Asn	ı Ile	e Glu	ı Asp	175		528	
50	Va]	Gli	n Let	1 Ala 180	a Asp	) His	з Туі	c Gli	n Gli 18	n Asr 5	ı Thi	r Pro	o Ile	e Gly 190	/ Asj	g GGC p Gly	576	
55	Pro	o Vai	l Lei 19!	ı Lev	ı Pro	o Asj	aA c	n Hi:	в <b>Т</b> у: 0	r Lei	ı Sei	r Th	r Gl: 20!	n Se: 5	r Al	C CTG		
	AG	C AA	A GA	c cc	C AA	C GA	AA E	G CG	C GA	T CA	C AT	G GT	C CT	G CT	G GA	G TTC		246

	Ser	Lys 210	Asp	Pro	Asn	Glu	Lys 215	Arg	Asp	His	Met	Val 220	Leu	Leu	Glu	Phe		
5				GCC Ala													720	
10				TCT Ser													768	
				GTT Val 260													816	
15				AAG Lys													864	
20				GTG Val													912	
25				GAC Asp													960	
30				CCA Pro													1008	
				AGT Ser 340													1056	
35				TGT Cys					Ile									
40			Arg	AAT Asn				Thr					Ala					
45		Glu		GTG Val			Glu					Met					•	
50				GGG Gly		Met					Lys					v Val		
				TTT Phe 420	Glu					, Ala					Arg			i
55	GGG	AAG	AAA	AAA .	TCT	' GGI	TGC	CTI	GTO	ттс	TGA						132	247

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Gly Lys Lys Ser Gly Cys Leu Val Leu
435 440
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5 (2) INFORMATION FOR SEQ ID NO:127:

- (i) SEQUENCE CHARACTERISTICS:
  - (A) LENGTH: 442 amino acids
  - (B) TYPE: amino acid
  - (C) STRANDEDNESS: single
  - (D) TOPOLOGY: linear
- (ii) MOLECULE TYPE: protein
- (v) FRAGMENT TYPE: internal

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(xi) SEQUENCE DESCRIPTION: SEQ ID NO:127:

	Met 1	Val	Ser	Lys	Gly 5	Glu	Glu	Leu	Phe _.	Thr 10	Gly	Val	Val	Pro	Ile 15	Leu
20	Val	Glu	Leu	Asp 20	Gly	Asp	Val	Asn	Gly 25	His	Lys	Phe	Ser	Val 30	Ser	Gly
	Glu	Gly	Glu 35	Gly	Asp	Ala	Thr	Tyr 40	Gly	Lys	Leu	Thr	Leu 45	Lys	Phe	Ile
25	Cys	Thr 50	Thr	Gly	Lys	Leu	Pro 55	Val	Pro	Trp	Pro	Thr 60	Leu	Val	Thr	Thr
	65		_			70					75			His		80
			, -		85					90				Val	95	
30	_			100					105					Arg 110		
		-	115					120					125	Leu		
35		130					135					140		Leu		
	145					150					155			Gln		160
	-				165					170				Asp	175	
40				180					185					190		Gly
			195					200					205			Leu
45		210					215					220	•			Phe
	225	•				230					235					Ser 240
	_				245					250					255	
50				260					265					270		Ile
			275					280		•			285	;		Phe
55		290	•				295	;				300	)			Leu
	Ala	Leu	Trp	Asp	Thr	Ala	Gly	Gln Gln	Glu	Asp	Tyr	Asp	Arg	Leu	Arg	Pro

																		•	
	305					310					315					320		•	
•		Ser	Tyr	Pro	Asp 325	Thr	Asp	Val	Ile	Leu 330	Met	Сув	Phe	Ser	Ile 335	Asp			
5	Ser	Pro	Asp	Ser 340		Glu	Asn	Ile	Pro 345		Lys	Trp	Thr	Pro 350	Glu	Val			
	Lys	His	Phe		Pro	Asn	Val	Pro 360		Ile	Leu	Val	Gly 365		Lys	Lys			
•	Asp	Leu 370		Asn	Asp	Glu	His		Arg	Arg	Glu	Leu 380		Lys	Met	Lys			
10		Glu	Pro	Val	Lys	Pro 390		Glu	Gly	Arg	Asp 395		Ala	Asn	Arg	Ile 400			
•	385 Gly	Ala	Phe	Gly	Tyr 405	Met	Glu	Cys	Ser	Ala 410		Thr	Lys	Asp	Gly 415				
45	Arg	Glu	Val				Ala	Thr	Arg		Ala	Leu	Gln	Ala 430		Arg			
15	Gly	Lys	Lys 435	420 Lys	Ser	Gly	Cys	Leu 440	Val	Leu				430					
				) INI	FORM	ATIO	N FOI	R SE	Q ID	NO:	128:								
20		(:	i) SI	EQUE	NCE (	CHAR	ACTE	RIST:	ics:		,								
			(A)	LENG	GTH: E: ni	114	0 ba	se pa											
25								_	e										
	(C) STRANDEDNESS: single (D) TOPOLOGY: linear  (ii) MOLECULE TYPE: cDNA																		
•	<pre>(ii) MOLECULE TYPE: cDNA (ix) FEATURE:  (A) NAME/KEY: Coding Sequence</pre>																		
30					ME/KI CATI			-	_	nce									
			(D	) OT	HER	INFO	RMAT	ION:				•						•	
35					ENCE														
															Pro	GAA Glu	4	18	
•	1				5					10					15				
40																CAG Gln		96	. •
				20					25					30			_		
45																GCG Ala	1.	44	
			35					40					45						
																AAG Lys	1	92	
50		50					55					60							
																CCA Pro	2	40	
55	65					70					. 75					80			
	GAG	CGA	GGC	AAG	ATG	AGA	GTC	CAC	: AAG	ATO	TCC	: AAC	GTC	: AAC	: AAC	GCC	2	88	249

	Glu	Arg	Gly	Lys	Met 85	Arg	Val	His	Lys	Ile 90	Ser	Asn	Val	Asn	Lys 95	Ala		
5		-					AAA Lys									_	336	
10							AAT Asn								_		384	
15					-		GAT Asp 135										432	
15							GGG Gly										480	
20		_					AAG Lys									GGC Gly	528	
25							CTG Leu										576	
30							CCC Pro										624	
0.5							TAC Tyr 215										672	
35							GAA Glu										720	
40							TAC Tyr										768	
45							CGC Arg										816	
50							GGG Gly										864	
			Val				GCC Ala 295	Asp					Gly			GTG Val	912	
55	AAC	TTC	AAG	ATC	CGC	CAC	AAC	ATC	GAG	GAC	GGC	AGC	GTG	CAG	CTC	GCC	960	250

										251							
	Asn 305	Phe	Lys	Ile	Arg	His 310	Asn	Ile	Glu	Asp	Gly 315	Ser	Val	Gln	Leu	Ala 320	•
5													CCC Pro				1008
10													AGC Ser				1056
15													GTG Val 365				1104
13		ATC Ile 370										TAA					1140
20			(2)	INI	FORM	TIOI	1 FOR	R SE	Q ID	NO:	129:						
25 .		i )	(B) (C)	LENG TYPI STR	E: ar ANDEI	379 mino ONESS	ACTEI amii acio S: s:	no ao i ingle	cids	٠						,	•
30		7)	Li) N 7) FI	RAGMI	ENT '	TYPE	: in	terna	al								
		()	(1) S	SEQUI	ENCE	DES	CRIP'	LION	: SE	Q ID	NO:	129:					•
35	1	_			5					.10					15	Glu Gln	
		_	_	20					25				Leu	30			
40	Gly		35 Gln	Ile	Glu	Asn		40 Glu	Glu	Asp	Phe	_	45 Asp	Gly	Leu	Lys	
		50 Met	Leu	Leu	Leu	Glu 70	55 Val	Ile	Ser	Gly	Glu 75	60 Arg	Leu	Ala	Lys	Pro 80	
45	65 Glu	Arg	Gly	Lys	Met 85		Val	His	Lys	Ile 90		Asn	Val	Asn	Lys 95	Ala	
40	Leu	Asp	Phe	Ile 100		Ser	Lys	Gly	Val	Lys	Leu	Val	Ser	Ile 110	Gly	Ala	
	Glu	Glu	Ile 115	Val	Asp	Gly	Asn	Val 120	Lys		Thr	Leu	Gly 125			Trp	
50	Thr	Ile 130	Ile	Leu	Arg	Arg	Asp 135		Pro	Val	Ala	Thr 140		Val	Ser	Lys	
	Gly 145		Glu	Leu	Phe	Thr 150	_	Val	Val	Pro	Ile 155		Val	Glu	Leu	Asp 160	
55	Gly	Asp	Val	Asn	Gly 165		Lys	Phe	Ser	Val 170		Gly	Glu	Gly	Glu 175	Gly	
	Asp	Ala	Thr	Tyr	Gly	Lys	Leu	Thr	Leu	Lys	Phe	Ile	Cys	Thr	Thr	Gly	

				180					185					190			
	Lys	Leu	Pro 195	Val	Pro	Trp	Pro	Thr 200	Leu	Val	Thr	Thr	Leu 205	Thr	Tyr	Gly	
5	Val	Gln 210	Cys	Phe	Ser	Arg	Tyr 215	Pro	Asp	His	Met	Lys 220	Gln	His	Asp	Phe	
	Phe 225	Lys	Ser	Ala	Met	Pro 230	Glu	Gly	Tyr	Val	Gln 235	Glu	Arg	Thr	Ile	Phe 240	
		Lys	Asp	qaA	Gly 245		Tyr	Lys	Thr	Arg 250	Ala	Glu	Val	Lys	Phe 255	Glu	
10	Gly	Asp	Thr	Leu 260		Asn	Arg	Ile	Glu 265		Lys	Gly	Ile	Asp 270	Phe	Lys	
	Glu	Asp	Gly 275		Ile	Leu	Gly	His 280		Leu	Glu	Tyr	Asn 285		Asn	Ser	
15	His	Asn 290	_	Tyr	Ile	Met	Ala 295		Lys	Gln	Lys	Asn 300		Ile	Lys	Val	
13	Asn 305	Phe	Lys	Ile	Arg	His 310		Ile	Glu	Asp	Gly 315		Val	Gln	Leu	Ala 320	
		His	Tyr	Gln	Gln 325		Thr	Pro	Ile	Gly 330	Asp	Gly	Pro	Val	Leu 335		
20	Pro	Asp	Asn			Leu	Ser	Thr				Leu	Ser	Lys 350		Pro	
	Asn	Glu		340 Arg	Asp	His	Met		345 Leu	Leu	Glu	Phę			Ala	Ala	
	Gly	Ile	355 Thr	Leu	Gly	Met	-	360 Glu	Leu	Tyr	ГÀÈ		365				
25		370					375										
				) INI						NO:	130:						
30		(:	(A)	EQUE!	GTH:	351	6 bas	se pa									
			(C)	TYPI	ANDE	DNES	S: s:	ingl	e								
				TOP													
35				MOLE FEAT		TYP	E: c	AND									
			(A)	IAN (	ME/K	EY:	Codi	ng S	eque	nce							•
40				) LOC ) OTI													
		(:	xi) :	SEQU	ENCE	DES	CRIP'	TION	: SE	Q ID	NO:	130:					
	ATG	GTG	AGC	AAG	GGC	GAG	GAG	CTG	TTC	ACC	GGG	GTG	GTG	CCC	ATC	CTG	48
45	Met 1	Val	Ser	Lys	Gly 5	Glu	Glu	Leu	Phe	Thr 10	Gly	Val	Val	Pro	Ile 15	Leu	
	GTC	GAG	CTG	GAC	GGC	GAC	GTA	AAC	GGC	CAC	AAG	TTC	AGC	GTG	TCC	GGC	96
50	Val	Glu	Leu	Asp 20	Gly	Asp	Val	Asn	Gly 25	His	Lys	Phe	Ser	Val	Ser	Gly	
	GAG	GGC	GAG	GGC	GAT	GCC	ACC	TAC	GGC	: AAG	CTG	ACC	CTG	AAG	TTC	ATC	144
																Ile	
55	TGC	ACC		GGC	AAG	CTG	CCC	GTG	CCC	TGG	CCC	. ACC	CTC	: GTG	ACC	. ACC	192
				-											,		252

	Cys	Thr 50	Thr	Gly	Lys	Leu	Pro 55	Val	Pro	Trp	Pro	Thr 60	Leu	Val	Thr	Thr	•	
5													GAC Asp				240	
10													TAC Tyr				288	
													ACC Thr				336	
15													GAG Glu 125				384	
20													AAG Lys				432	
25												Asp	AAG Lys				480	
30													GAG Glu				528	
													ATC Ile			GGC Gly	576	
35									Tyr							CTG Leu	624	•
40													Leu			TTC Phe	672	
45		Thr					Thr					Glu				TCC Ser 240	720	
50						Ala					Glu					CCC Pro	768	
					Ala					Pro					Glr	GAC Asp	816	
55	GAG	CTI	GAC	TTC	TCC	: ATC	CTC	TTC	GAC	TĄT	GAG	TAT	TTC	TAA 3	ccc	G AAC	864	253

	Glu	Leu	Asp 275	Phe	Ser	Ile	Leu	Phe 280	Asp	Tyr	Glu	Tyr	Leu 285	Asn	Pro	Asn		
5														TCC Ser	_		912	
10										_				TAC Tyr			960	
														GAG Glu			1008	
15														GCA Ala 350			1056	
20														GAA Glu			1104	
25														CTG Leu			1152	
. 30														ACC Thr			1200	
														AGC Ser			1248	
35														TCC Ser 430			1296	
40				Cys										GAC Asp			1344	
45			Phe										Arg	ACC Thr		CCA Pro	1392	
50		Met										Ser				CGC Arg 480	1440	
						Arg					Ser					GCC	1488	
55	AAG	CGG	AGG	CAT	TCG	TGC	GCC	GAG	GCC	TTG	GTT	GCC	CTG	CCG	CCC	GGA	1536	254

									•									
	Lys	Arg	Arg	His 500	Ser	Cys	Ala	Glu	Ala 505	Leu	Val	Ala	Leu	Pro 510	Pro	Gly		
5														TCA Ser			1584	
10														CCT Pro			1632	
15														ACG Thr			1680	
														GAC Asp			1728	
20														CAC His 590			1776	
25												Gly		AGG Arg			1824	
30														CCC Pro			1872	
35														GCA Ala			1920	
														TAC Tyr			1968	
40														TAT Tyr 670			2016	•
45														CAC His			2064	
50													Gly	CTT Leu		_	2112	
55		Ile										Pro		GCC Ala			2160	
JJ	CAG	GTG	CAC	CGA	ATC	ACG	GGG	AAĄ	ACT	GTC	ACC	ACC	ACC	AGC	TAT	GAG	2208	255

									•	_00								•
	Gln	Val	His	Arg	Ile 725	Thr	Gly	Lys	Thr	Val 730	Thr	Thr	Thr	Ser	Tyr 735	Glu		
5				GGC Gly 740													2256	
10				AGG Arg												AGA Arg	2304	
15				ATT Ile													2352	
15				GTG Val													2400	
20				GTC Val													2448	
25				GCT Ala 820									Gln				2496	
30				GTC Val													2544	
05				GAG Glu													2592	
35		Gln		TGG Trp													2640	: *
40				CTT Leu													2688	
45				GTA Val 900													2736	
50				CCT Pro												AAG Lys	2784	
55			Pro					Asp					Cys			ACC	2832	
55	CAT	GGA	GGC	CTG	GGG	AGC	CAG	CCT	TAC	TAC	ccc	CAG	CAC	CCG	ATG	GTG	2880	256

																	•	
•	His 945	Gly	Gly	Leu	Gly	Ser 950	Gln	Pro	Tyr	Tyr	Pro 955	Gln	His	Pro	Met	Val 960		
5			TCC Ser														2928	
40			ACG Thr	Gly					Asp					Gln			2976	
10			GCC														3024	
15			Ala 995			•	3	1000				:	1005	•	,			
	Leu		TAT Tyr			Pro					Ala						3072	
20			CAC His		Ser					Ala					Gln		3120	
25			CTG Leu	Leu					Thr					Ser			3168	
			TAC Tyr		Pro			Gln					Gly				3216	
30		Phe	CAG Gln	CAC	ATC		Tyr	TGC Cys	GAG			Ala	CCA Pro	GGC			3264	
35		CCT	1075 GGC				GTC					AGG					3312	
		1090	_				1095					1100		•		Gly		
40	TCC Ser 1105	Tyr	CCC Pro		Val					Asn		Thr			Arg		3360	
45				Gly		Pro			Asp		Lys					GCG Ala	3408	
50			Thr		Lys			Gln		Leu					Leu	GAT Asp	3456	
				Glu			Arg		Glu					Pro		AGA Arg	3504	
55	TAA	CAG	ACG			٠											3516 25	57
																	~`	•

Asn Gln Thr 1170

55

(2) INFORMATION FOR SEQ ID NO:131: 5 (i) SEQUENCE CHARACTERISTICS: (A) LENGTH: 1171 amino acids (B) TYPE: amino acid (C) STRANDEDNESS: single 10 (D) TOPOLOGY: linear (ii) MOLECULE TYPE: protein (v) FRAGMENT TYPE: internal 15 (xi) SEQUENCE DESCRIPTION: SEQ ID NO:131: Met Val Ser Lys Gly Glu Glu Leu Phe Thr Gly Val Val Pro Ile Leu 10 Val Glu Leu Asp Gly Asp Val Asn Gly His Lys Phe Ser Val Ser Gly 20 25 Glu Gly Glu Gly Asp Ala Thr Tyr Gly Lys Leu Thr Leu Lys Phe Ile Cys Thr Thr Gly Lys Leu Pro Val Pro Trp Pro Thr Leu Val Thr Thr 25 Leu Thr Tyr Gly Val Gln Cys Phe Ser Arg Tyr Pro Asp His Met Lys 70 Gln His Asp Phe Phe Lys Ser Ala Met Pro Glu Gly Tyr Val Gln Glu 90 85 Arg Thr Ile Phe Phe Lys Asp Asp Gly Asn Tyr Lys Thr Arg Ala Glu 30 105 Val Lys Phe Glu Gly Asp Thr Leu Val Asn Arg Ile Glu Leu Lys Gly 120 Ile Asp Phe Lys Glu Asp Gly Asn Ile Leu Gly His Lys Leu Glu Tyr . 140 35 135 Asn Tyr Asn Ser His Asn Val Tyr Ile Met Ala Asp Lys Gln Lys Asn 150 155 Gly Ile Lys Val Asn Phe Lys Ile Arg His Asn Ile Glu Asp Gly Ser 170 165 Val Gln Leu Ala Asp His Tyr Gln Gln Asn Thr Pro Ile Gly Asp Gly 40 185 Pro Val Leu Leu Pro Asp Asn His Tyr Leu Ser Thr Gln Ser Ala Leu 205 200 Ser Lys Asp Pro Asn Glu Lys Arg Asp His Met Val Leu Leu Glu Phe 215 45 Val Thr Ala Ala Gly Ile Thr Leu Gly Met Asp Glu Leu Tyr Lys Ser 230 235 Gly Leu Arg Ser Arg Ala Met Asn Ala Pro Glu Arg Gln Pro Gln Pro 245 250 . Asp Gly Gly Asp Ala Pro Gly His Glu Pro Gly Gly Ser Pro Gln Asp 50 265 Glu Leu Asp Phe Ser Ile Leu Phe Asp Tyr Glu Tyr Leu Asn Pro Asn

275 280 285 Glu Glu Glu Pro Asn Ala His Lys Val Ala Ser Pro Pro Ser Gly Pro

Ala Tyr Pro Asp Asp Val Met Asp Tyr Gly Leu Lys Pro Tyr Ser Pro

	305					310					315					320
	Leu	Ala	Ser	Leu	Ser	Gly	Glu	Pro	Pro	Gly	Arg	Phe	Gly	Glu	Pro	Asp
					325					330					335	
	Arg	Val	Gly	Pro	Gln	Lys	Phe	Leu	Ser	Ala	Ala	Lys	Pro	Ala	Gly	Ala
5				340					345					350		
	Ser	Gly	Leu	Ser	Pro	Arg	Ile	Glu	Ile	Thr	Pro	Ser	His	Glu	Leu	Ile
•			355					360			•		365			
•	Gln	Ala	Val	Gly	Pro	Leu	Arg	Met	Arg	Asp	Ala	Gly	Leu	Leu	Val	Glu
		370					375					380				
10	Gln	Pro	Pro	Leu	Ala		Val	Ala	Ala	Ser		Arg	Phe	Thr	Leu	
	385	•				390			_		395			_	_	400
	Val	Pro	Gly	Phe		Gly	Tyr	Arg	Glu		Leu	Cys	Leu	Ser		Ala
				_	405		_	_,		410		-1	<b>51.</b> -	0	415	M+ +++
	Ser	Ser	Gly		Ser	Ala	Ser	Phe		ser	Asp	Thr	Pne		PIO	Tyr
15		_	_	420		_	<b>5</b>	•	425	<b>a</b> 1	<u>ن</u>	D	N	430	T 033	Cura
	Thr	Ser		Cys	vaı	ser	Pro		Asn	GTA	GIY	Pro	445	Asp	Leu	cys
		Gln	435	<b>~</b> 1	3	T1_	D	440	773.0	TT	Cor	Dro		mh ~	Car	Pro
	Pro		Pne	GII	ASII	116	455	Ala	HIS	IYL	Ser	460	Arg	1111	Ser	FIC
30	T3 -	450 Met	C 0 20	Dwo	7~~	Th~		T 011	ת 1 ת	Glu	λάn		Cve	Len	Glv	Δrα
20	465	Mer	ser	PIO	Arg	470	Ser	Tie a	AIA	Giu	475	Jei	Cys	n-u	Cly	480
		Ser	Dro	Val	Pro		Pro	Δla	Ser	Ara		Ser	Ser	Pro	Glv	
	mra	DCI	110	VUL	485	g		1114	001	490					495	
	Lvs	Arg	Ara	His		Cvs	Ala	Glu	Ala		Val	Ala	Leu	Pro	Pro	Gly
25	<i>,</i>	••••	9	500		7			505					510		_
	Ala	Ser	Pro		Arg	Ser	Arg	Ser	Pro	Ser	Pro	Gln	Pro	Ser	Ser	His
			515		_		_	520					525			
	Val	Ala	Pro	Gln	Asp	His	Gly	Ser	Pro	Ala	Gly	Tyr	Pro	Pro	Val	Ala
		530			_		535	,				540				
30	Gly	Ser	Ala	Val	Ile	Met	Asp	Ala	Leu	Asn	Ser	Leu	Ala	Thr	Asp	Ser
	545					550			•		555					560
	Pro	Cys	Gly	Ile	Pro	Pro	Lys	Met	Trp	Lys	Thr	Ser	Pro	Asp		Ser
					565					570				•	575	_
	Pro	Val	Ser			Pro	Ser	Lys		Gly	Leu	Pro	Arg		11e	Tyr
35				580					585			~ 7	<b>~</b> 1	590	7	n
	Pro	Ala		Glu	Phe	Leu	GIY		Cys	GIu	Gin	GIY		Arg	Arg	ASII
	_	- 1 -	595	a1	0	<b>T</b> 1.	7	600	*** 1	Dwa	Dvo	mb~	605	Dro	Tare	Pro
	Ser	Ala	Pro	GIU	ser	ire			vaı	PIO	PIO	620	пр	FIO	БуЗ	FIO
40	T	610 Val	Dwo	אות	Tla	Drio	615		car	מוז	Dro		Thr	Δla	Ser	Leu
40	் 625		PIO	Ата	116	630		Сув	Ser	116	635	Vul	1111			640
		Pro	T.e.11	Glu	Trn			Ser	Ser	Gln		Glv	Ser	Tvr	Glu	
	PLO	PIU	пец	Giu	645		пси	DCI	DCI	650		J_1		-1-	655	
	Ara	Ile	Glu	Val			Lvs	Pro	His			Ala	His	Tyr		
45	**** 9		0.10	660			-1-		665		5			670		
	Glu	Gly	Ser			Ala	Val	Lys			Thr	Gly	Gly	His	Pro	Val
		1	675		•			680				-	685			
	Val	Gln	Leu	His	Gly	Tyr	Met	Glu	Asn	Lys	Pro	Leu	Gly	Leu	Gln	Ile
		690			•	-	695			_		700				
50	Phe	Ile	Gly	Thr	Ala	Asp	Glu	Arg	Ile	Leu	Lys	Pro	His	Ala	Phe	Tyr
	705					710					715					720
	Gln	Val	His	Arg	Ile	Thr	Gly	Lys	Thr	Val	Thr	Thr	Thr	Ser		
					725					730					735	
	Lys	Ile	Val	Gly	Asr	Thr	Lys	: Val			Ile	Pro	Leu			. Lys
55				740					745				_	750		
	Asn	Asn	Met	Arg	Ala	Thr	: Ile	Asp	Cys	Ala	Gly	Ile	. Lev	грув	ь	Arg

			755					760					765			
		770	Asp				775					780				
5	Asn 785	Thr	Arg	Val	Arg	Leu 790	Val	Phe	Arg	Val	His 795	Ile	Pro	Glu	Ser	Ser 800
	Gly	Arg	Ile		Ser 805		Gln	Thr	Ala	Ser 810	Asn	Pro	Ile	Glu	Cys 815	Ser
	Gln	Arg	Ser	Ala 820	His	Glu	Leu	Pro	Met 825	Val	Glu	Arg	Gln	Asp 830	Thr	Asp
10	Ser	Cys	Leu 835	Val	Tyr	Gly	Gly	Gln 840	Gln	Met	Ile	Leu	Thr 845	Gly	Gln	Asn
		850	Ser			-	855					860			_	_
15	865		Ile			870					875					880
			Meț		885					890					895	
	_		Pro	900	_				905					910	•	
20	_		Gln 915				•	920	_				925			
		930	Pro				935					940				
25	945		Gly			950					955			•		960
			Ser		965					970					975	
00			Thr	980					985					990		
30			Ala 995			_		1000		_		:	1005			
		1010					1015		•			1020				
35	025		His			1030					1035					1040
			Leu		1045					1050					1055	
40				1060					1065					1070		
40			Gln 1075					1080					1085			
		1090	Gly				1095					1100				
45	105	_	Pro			1110					1115					1120
			Asn		1125					1130					1135	
	_			1140					1145					1150		
50	-		Asn 1155	GLu	тте	тте		Lys 1160		Pne	ser		1165		ATS	Arg
		Gln 1170														

55 (2) INFORMATION FOR SEQ ID NO:132:

5			(A) (B) (C)	LENG TYPE STRA	TH: : nu NDED	HARA 3546 clei NESS	bas c ac : si	e pa id ngle	irs								•
· .			i) M x) F			TYPE	: cD	AA				•					
10			(B)	roc	ATIC	Y: C N: 1 NFOR	3	543	quen	.ce							
45		(x	i) S	EQUE	NCE	DESC	RIPT	: NOI	SEÇ	ID	NO:1	32:					
15		AAC Asn															48
20		CAC His															96
25		TTC Phe															144
30		AAG Lys 50															192
35		GAC Asp															240
		CCC Pro															288
40		CTG Leu															336
45		GAG Glu															384
50		ATG Met 130															432
55		GCC Ala					Phe										480
	TAC	CGC	GAG	CCG	CTT	TGC	TTG	AGC	CCC	GCI	AGC	AGC	GGC	TCC	TCT	GCC	528

•	Tyr	Arg	Glu	Pro	Leu 165	Сув	Leu	Ser	Pro	Ala 170	Ser	Ser	Gly	Ser	Ser 175	Ala	
•	AGC	TTC	ATT	TCT	GAC	ACC	TTC	TCC	CCC	TAC	ACC	TCG	CCC	TGC	GTC	TCG	576
5		Phe															
	CCC	AAT	AAC	GGC	GGG	CCC	GAC	GAC	CTG	TGT	CCG	CAG	TŤT	CAA	AAC	ATC	624
10	Pro	Asn	Asn 195	Gly	Gly	Pro	Asp	Asp 200	Leu	Cys	Pro	Gln	Phe 205	Gln	Asn	Ile	
	CCT	GCT	CAT	TAT	TCC	CCC	AGA	ACC	TCG	CCA	ATA	ATG	TCA	CCT	CGA	ACC	672
15	Pro	Ala 210	His	Tyr	Ser	Pro	Arg 215	Thr	Ser	Pro	Ile	Met 220	Ser	Pro	Arg	Thr	
13	AGC	CTC	GCC	GAG	GAC	AGC	TGC	CTG	GGC	CGC	CAC	TCG	ccc	GTG	ccc	CGT	720
		Leu										Ser					
20	CCG	GCC	TCC	CGC	TCC	TCA	TCG	CCT	GGT	GCC	AAG	CGG	AGG	CAT	TCG	TGC	768
		Ala	-														
	GCC	GAG	GCC	TTG	GTT	GCC	CTG	CCG	CCC	GGA	GCC	TCA	CCC	CAG	CGC	TCC	816
25	Ala	Glu	Ala	Leu 260	Val	Ala	Leu	Pro	Pro 265	Gly	Ala	Ser	Pro	Gln 270	Arg	Ser	
	CGG	AGC	CCC	TCG	CCG	CAG	CCC	TCA	TCT	CAC	GTG	GCA	CCC	CAG	GAC	CAC	864
30	Arg	Ser	Pro 275	Ser	Pro	Gln	Pro	Ser 280	Ser	His	Val	Ala	Pro 285	Gln	Asp	His	
	GGC	TCC	CCG	GCT	GGG	TAC	CCC	CCT	GTG	GCT	GGC	TCT	GCC	GTG	ATC	ATG	912
	Gly	Ser 290	Pro	Ala	Gly	Tyr	Pro 295	Pro	Val	Ala	Gly	Ser 300	Ala	Val	Ile	Met	
35	~~-		ama			am a			~- ~				~~~			000	0.50
		GCC Ala												_			960
	305					310			<u>-</u> -		315	-2-	2			320	
40	AAG	ATG	TGG	AAG	ACC	AGC	CCT	GAC	CCC	TCG	CCG	GTG	TCT	GCC	GCC	CCA	1008
	Lys	Met	Trp	Lys	Thr 325	Ser	Pro	Asp		Ser 330	Pro	Val	Ser	Ala	Ala 335	Pro	
	TCC	AAG	GCC	GGC	CTG	CCT	CGC	CAC	ATC	TAC	CCG	GCC	GTG	GAG	TTC	CTG	1056
45	Ser	Lys	Ala	Gly. 340	Leu	Pro	Arg	His	11e 345	Tyr	Pro	Ala	Val	Glu 350	Phe	Leu	
	. GGG	CCC	TGC	GAG	CAG	GGC	GAG	AGG	AGA	AAC	TCG	GCT	CCA	GAA	TCC	ATC	1104
50	Gly	Pro	Сув 355	Glu	Gln	Gly	Glu	Arg 360	Arg	Asn	Ser	Ala	Pro 365	Glu	Ser	Ile	
	CTG	CTG	GTT	CCG	CCC	ACT	TGG	CCC	AAG	CCG	CTG	GTG	CCT	GCC	ATT	CCC	1152
	Leu		Val	Pro	Pro	Thr	_	Pro	Lys	Pro	Leu		Pro	Ala	Ile	Pro	
55		370					375					380					
55	ATC	TGC	AGC	ATC	CCA	GTG	ACT	GCA	TCC	CTC	CCT	CCA	CTT	GAG	TGG	CCG	1200

	Ile 385	Cys	Ser	Ile	Pro	Val 390	Thr	Ala	Ser	Leu	Pro 395	Pro	Leu	Glu	Trp	Pro 400		
5				CAG Gln													1248	
10			His	CAC His 420													1296	
15				CCA Pro										_	_		1344	
15				AAG Lys													1392	
20				CTT Leu													1440	
25				GTC Val	-												1488	
30				GAG Glu 500											_	_	1536	
25				GCG Ala													1584	
35				GAG Glu													1632	
40	GTT Val 545			GTT Val													1680	. •
45				TCT													1728	
50										qaA					Tyr	GGC Gly	1776	
									Gln					Glu		Lys	1824	
55	GTT	GTG	TTT	ACT	GAG	AAG	ACC	ACA	GAT	GGA	CAG	CAA	. ATT	' TGG	GAG	ATG	1872	263

	Val	Val 610	Phe	Thr	Glu	Lys	Thr 615	Thr	Asp	Gly	Gln	Gln 620	Ile	Trp	Glu	Met	
5					GAT Asp												1920
10					TAT Tyr 645											Val	1968
·:					ATC Ile											CAC His	2016
15					CCA Pro												2064
20					CTG Leu												2112
25					CCC Pro												2160
30		_			ATG Met 725												2208
35				_	CGC Arg												2256
55					AGC Ser												2304
40					GCC Ala												2352
45					GGC Gly												2400
50					CAG Gln 805												2448
EE					CGC Arg												2496
55	TAC	TGC	GAG	AAT	TTC	GCA	CCA	GGC	ACC	ACC	AGA	CCT	GGC	CCG	ccc	CCG	2544

,	Tyr	Cys	Glu 835	Asn	Phe	Ala	Pro	Gly 840	Thr	Thr	Arg	Pro	Gly 845	Pro	Pro	Pro	,	
5				GGT Gly													2592	
10				AAT Asn						Ala							2640	
45				CAA Gln													2688	
15				TTG Leu 900												_	2736	
20				TTT Phe											_		2784	
25				GTA Val												_	2832	
30		•		GAG Glu													2880	
0.5				GAC Asp											_		2928	
35				GCC Ala 980										_			2976	
40				CTG Leu			Pro					Val					3024	
45	Tyr			CAG Gln		Phe					Asp		Met			CAC	3072	
50		Phe			Ser	,	_			Gly		Val				ACC Thr	3120	
				ГÀв		Asp					Thr				_	AAG Lys	3168	
55	TTC	GAG	GGC	GAC	ACC	ÇTG	GTG	AAC	CGC	: ATC	GAG	CTC	AAG	GGC	ATC	GAC	3216	265

	Phe	Glu		Asp 060	Thr	Leu	Val		Arg 1065	Ile	Glu	Leu	_	Gly .070	Ile	Asp	
5		AAG Lys					Ile					Leu					3264
10	Asn	AGC Ser 1090				Tyr					Lys						3312
15		GTG Val			Lys					Ile					Val		3360
		GCC Ala		His					Thr					Gly			3408
20 .		CTG Leu	Pro					Leu					Ala				3456
25		CCC Pro					Asp					Leu					3504
30	Ala	GCC Ala 1170				Leu					Leu			AAT			3546
			(2)	INI	FORM	TION	, FOI	R SEC	) ID	NO:	133:						
35		(1	(A) (B) (C)	EQUENCE TYPE STRA	ETH: E: an ANDEI	1181 nino ONESS	l am: acid 3: s:	ino a i ingle	acida	3							
40			li) N	OLE RAGMI	CULE	TYPE	E: pi	rote:									
				EQUI						Q ID	NO:	133:					
45	Met 1	Asn	Ala	Pro	Glu	Arg	Gln	Pro	Gln	Pro	Āsp	Gly	Gly	Asp	Ala 15	Pro	
		His	Glu	Pro 20	Gly	Gly	Ser	Pro	Gln 25		Glu	Leu	Asp	Phe 30		Ile	
50		Phe Lys	35					40					45				
		50 Asp					55					60					٠
55	65	Pro				70		-			75					80	٠

									•	201						
					85					90					95	
	Phe	Leu	Ser	Ala 100	Ala	Lys	Pro	Ala	Gly 105	Ala	Ser	Gly	Leu	Ser 110	Pro	Arg
5	Ile	Glu	Ile 115		Pro	Ser	His	Glu 120		Ile	Gln	Ala	Val 125		Pro	Leu
	Arg	Met 130	Arg	Asp	Ala	Gly	Leu 135	Leu	Val	Glu	Gln	Pro 140	Pro	Leu	Ala	Gly
	Val 145	Ala	Ala	Ser	Pro	Arg 150	Phe	Thr	Leu	Pro	Val 155	Pro	Gly	Phe	Glu	Gly 160
10	Tyr	Arg	Glu	Pro	Leu 165	Cys	Leu	Ser	Pro	Ala 170	Ser	Ser	Gly	Ser	Ser 175	Ala
		Phe		180					185	-				190		
15		Asn	195			·		200					205			
		Ala 210					215					220			-,	
	225	Leu				230				_	235					240
20	,	Ala	•		245				_	250	-	_			255	
		Glu		260					265					270		
25		Ser	275					280					285			
		Ser 290					295					300				
20	305	Ala				310			_		315	-	_			320
30	-	Met		_	325			_		330					335	
		Lys		340					345	-			•	350		
35		Pro Leu	355					360	-				365			
		370 Cys					375		_			380				
40	385					390					395					400 Pro
					405	_		_		410					415	Ala
				420				-	425			_		430		Tyr
45			435					440					445			Asp
		450		_			455					460	_			Thr
50	465					470	•			_	475					480 Thr
					485				-	490	_				495	Thr
				500					505					510		Leu
55	Arg	Lys	515 Gly	Glu	Thr	Asp	Ile	520 Gly	Arg	Lys	Asn	Thr	525 Arg	Val	Arg	Leu

		530					535					<b>540</b>				
	V-1		Arg	V=1	uic	Tla		G111	Co~	Co~	01	540	T1.	tro 1	Co=	T 011
	545	FIIC	AT 9	val	1172	550	PIO	GIU	Ser	ser	555	Arg	116	vai	Ser	560
		Thr	Ala	Ser	Asn		Tle	Glu	Cvs	Ser		Ara	Ser	Δla	Hie	
5					565			<b>01</b> u	Cyo	570	OIII	AI 9	JCI	ALU	575	OIL
Ū	Leu	Pro	Met	Val		Ara	Gln	asp	Thr		Ser	Cvs	Len	Val		Glv
				580		5		<u>F</u>	585	·p	501	Cyc	<b>200</b>	590	- 7 -	O.J
	Gly	Gln	Gln			Leu	Thr	Glv		Asn	Phe	Thr	Ser		Ser	Lvs
	-		595					600			_		605			-3 -
10	Val	Val	Phe	Thr	Glu	Lys	Thr	Thr	qsA	Gly	Gln	Gln		Trp	Glu	Met
		610					615		-	-		620		•		
	Glu	Ala	Thr	Val	Asp	Lys	Asp	Lys	Ser	Gln	Pro	Asn	Met	Leu	Phe	Val
	625					630					635					640
·	Glu	Ile	Pro	Glu	Tyr	Arg	Asn	Lys	His	Ile	Arg	Thr	${\tt Pro}$	Val	Lys	Val
15					645				•	650					655	
	Asn	Phe	Tyr		Ile	Asn	Gly	ràs	Arg	Lys	Arg	Ser	Gln	Pro	Gln	His
	_		_	660	_	_			665					670		
	Phe	Thr	Tyr	His	Pro	Val			Ile	Lys	Thr	Glu		Thr	Asp	Glu
20	<b></b>	<b>&gt;</b>	675	mb	7	<b>77</b> -		680	_		•		685	_		_
20	Tyr	690	Pro	THE	Leu	тте		ser	Pro	Thr	Hls	-	GIA	Leu	GIÀ	ser
	Gln		Tyr	<b>Пл. г.х.</b>	Dro	Cl n	695 Uic	Dro	Mot	17-1	77.	700	C . ~	D=0	Co~	ė.
	705	FIO	TYL	TYL	FIU	710	nis	PIO	Met	val	715	GIU	Ser	PIO	Ser	720
		Val	Ala	Thr	Met		Pro	Cve	Gln	Gln		Ara	Thr	Glv	T.011	
25					725			<b>-</b> 12	0111	730	1 110		****	Cly	735	
	Ser	Pro	Asp	Ala	Arg	Tyr	Gln	Gln	Gln		Pro	Ala	Ala	Val		Tyr
			_	740		_			745					750		•
	Gln	Arg	Ser	Lys	Ser	Leu	Ser	Pro	Ser	Leu	Leu	Gly	Tyr	Gln	Gln	Pro
			755					760					765			
30	Ala	Leu	Met	Ala	Ala	Pro	Leu	Ser	Leu	Ala	Asp	Ala	His	Arg	Ser	Val
		770					775					780				
		Val	His	Ala	Gly		Gln	Gly	Gln	Ser		Ala	Leu	Leu	His	
	785	_		_		790		_	_		795		_	_		800
25	ser	Pro	Thr	Asn		Gin	Ala	Ser	Pro		He	His	Tyr	Ser		Thr
35	7 ~~	C15	C1-	T 0.1	805	O	<b>61</b>	0	174 -	810	<b>03</b>	Dh a	<b>~</b> 3	774 -	815	Mak
	ASII	GIII	Gln	820	Arg	Cys	GIY	ser	825	GII	GIU	Pne	GIII	830	TIE	Met
	יינים	CVR	Glu		Dhe	Δla	Dro	Glv		Thr	7 ~~	Dro	G1v		Pro	Pro
	-1-	C	835		1110	ALU	110	840	TILL	1111	ALG	FIO	845	FIO	FIO	FIG
40	Val	Ser	Gln	Gly	Gln	Arg	Leu		Pro	Glv	Ser	Tvr		Thr	Val	Ile
		850		•			855					860				
	Gln	Gln	Gln	Asn	Ala	Thr	Ser	Gln	Arg	Ala	Ala	Lys	Asn	Gly	Pro	Pro
	865					870			_		875	-		•		880
•	Val	Ser	Asp	${\tt Gln}$	Lys	Glu	Val	Leu	Pro	Ala	Gly	Val	Thr	Ile	Lys	Gln
45					885					890					895	
	Glu	Gln	Asn	Leu	Asp	Gln	Thr	Tyr	Leu	Asp	Asp	Val	Asn	Glu	Ile	Ile
				900					905					910		
	Arg	Lys	Glu	Phe	Ser	Gly	Pro		Ala	Arg	Asn	Gln	Thr	Arg	Ile	Leu
		_	915					920					925			_
50	Gln		Thr	Val	Pro	Arg		Arg	Asp	Pro	Pro		Ala	Thr	Met	Val
	0	930	<b>~</b> 3	<b>~</b> 1	<b>a</b> 3.	•	935	<b></b> 1				940		_		
		rÀs	стХ	GIU	GIU		ьиe	Tnr	GIA	val		Pro	тте	ьeu	vaı	Glu
	945	Δου	Glv	Aen	T _e T	950	G1++	u:-	T	Dhe	955	17-1	e.~	<b>G1</b>	<b>@1</b>	960
55	neu	vaħ	GTA	vaħ	965	WOII	GTÅ	uTR	пÃ2	970	ber	val	SEL	GTÅ	975	Gly
00	Glu	G]v	Asp	Ala		Tvr	G] v	Ive	Len		Lev	Lve	Phe	Tle		Thr
		1	E-			- 2 -	1		~~~			-,-			-1-	

				980					985					990				•	
	Thr	Gly	Lys 995	Leu	Pro	Val		Trp 000	Pro	Thr	Leu		Thr .005		Leu	Thr			
5	Tyr 1	Gly 010	Val	Gln	Cys		Ser .015	Arg	Tyr	Pro		His 020	Met	Lys	Gln	His			
	Asp 025	Phe	Phe	Lys		Ala .030	Met	Pro	Glu		Tyr 035	Val	Gln	Glu		Thr .040			
Ť	Ile	Phe	Phe		Asp	Asp	Gly	Asn		Lys .050	Thr	Arg	Ala		Val 1055	Lys			
10	Phe	Glu				Leu	Val				Glu	Leu				Asp			
	Phe	-			Gly	Asn				His	Lys		Glu 1085	Tyr	Asn	Tyr			
	Asn	Ser		Asn	Val		Ile		Ala	Asp		Gln		Asn	Gly	Ile	•		
15	l Lys	.090 Val	Asn	Phe	Lys		L095 Arg	His	Asn	Ile		Asp	Gly	Ser	Val	Gln			
	105				1	110				1	.115				1	120			
					125				1	L130				1	1135		,		
20	Leu	Leu		Asp 1140	Asn	HIS	ıyr		Ser 1145	Thr	GIN	ser		150	261	ъyв			
	Asp			Glu	Lys	Arg			Met	Val	Leu		Glu 1165	Phe	Val	Thr			
	Ala		.155 Gly	Ile	Thr	Leu		1160 Met	Asp	Glu	Leu								
25	1	170				:	1175				:	1180							
			(2)	INE	FORM	ATIO	1 FOI	R SE	Q ID	NO:	L34:								
		13	١ ٥٠		10D /	777 X Y Y		- * cm									·		
30		(1		LENO															
				TYPE											•				
				TOP				-	E								•		
35				MOLE		TYP	E: cl	DNA											
•		i)		FEAT					٠										
				) NAI ) LO				_	_	nce									
40			• • •	OTI															
		(2	ci) :	SEQUI	ENCE	DES	CRIP'	TION	: SE	Q ID	NO:	134:							
																CTG		48	
45		Val	Ser	Lys		Glu	Glu	Leu	Phe		Gly	Val	Val	Pro	Ile 15	Leu			
	1				5					10					15			•	
																GGC		96	
50	Val	GIU	Leu	Asp 20	GIY	Asp	vaı	Asn	25	HIS	гàг	Pne	Ser	30	Ser	Gly			
																ATC	. 1	44	
	Glu	Gly		Gly	Asp	Ala	Thr	Tyr	Gly	Lys	Leu	Thr	Leu 45	Lys	Phe	Ile			
55			35					40					33						
	TGC	ACC	ACC	GGC	AAG	CTG	CCC	GTG	CCC	TGG	CCC	ACC	CTC	GTG	ACC	ACC	1	192	269
																		4	UJ

	Cys	Thr 50	Thr	Gly	Lys	Leu	Pro 55	Val	Pro	Trp	Pro	Thr 60	Leu	Val	Thr	Thr		
5				GGC Gly													240	
10				TTC Phe												Glu	288	
15				TTC Phe 100													336	
				GAG Glu													384	
20				AAG Lys													432	
25				AGC Ser													480	
30				GTG Val													528	
35				GCC Ala 180													576	
				CTG Leu													624	
40				CCC Pro													672	
45				GCC Ala								_					720	
50				TCT Ser													768	
55				GAG Glu 260													816	
	GAC	GAG	CTG	GAG	CTG	GAG	TTG	GAT	CAG	AAG	GAC	GAA	CTG	ATC	CAG	AAG	864	270

	Asp	Glu	Leu 275	Glu	Leu	Glu	Leu	Asp 280	Gln	Lys	Asp	Glu	Leu 285	Ile	Gln	Lys	•
5												ATC Ile 300					912
10												CAG Gln					960
												GCC Ala			_	_	1008
15												AAG Lys			_		1056
20												GAC Asp					1104
25	Leu											TGT Cys 380				_	1152
30												GGA Gly					1200
35	. CTG Leu											GTT Val					1248
												TTT Phe					1296
40												AAG Lys					1344
45												CAA Gln 460					1392
50		Thr										Glu				AGC Ser 480	1440
e e						Ser					Ile					GCT	1488
55	GAT	GTC	CTT	GAA	GAG	ACC	CAC	TAT	' GAA	TAA	GGA	GAA	TAT	' ATI	' ATC	AGG	1536 2

	Asp	Val	Leu	Glu 500	Glu	Thr	His	Tyr	Glu 505	Asn	Gly	Glu	Tyr	Ile 510		Arg	
	CAA	GGT	GCA	AGA	GGG	GAC	ACC	ייייכי	ւրար	ΑΤС	איזכי	AGC	ααα	GGA	ACG	ATD.	1584
5												Ser					1304
•		<b>-</b> 1	515	5	1			520					525	1			
	AAT	GTC	ACT	CGT	GAA	GAC	TCA	CCG	AGT	GAA	GAC	CCA	GTC	TTT	CTT	AGA	1632
	Asn	Val	Thr	Arg	Glu	Asp	Ser	Pro	Ser	Glu	Asp	Pro	Val	Phe	Leu	Arg.	
10		530					535					540					
												GCC					1680
		Leu	GIA	Lys	Gly		Trp	Phe	GIA	Glu,	_	Ala	Leu	Gin	GIY		
15	545					550					555					560	
	CAT	GTG	ACA	מסמ	GCA	ממכ	GTA	ייייי ע	GCT	GCA	۵۵۵	GCT	СТД	ACC	ייפר	ملسك	1728
												Ala					1,20
	···				565					570					575		
							***										
20	GTG	ATT	GAC	AGA	GAC	TCT	TTT	AAA	CAT	TTG	ATT	GGA	GGG	CTG	GAT	GAT	1776
	Val	Ile	Asp	Arg	Asp	Ser	Phe	Lys	His	Leu	Ile	Gly	Gly	Leu	Asp	Asp	
				580				-	585					590			•
		m.cm				m = m	<i>-</i>	~~ m		<b></b>							1004
25												AAA					1824
25	vaı	261	595	nys	MIG	TAT	GIU	600	Ald	GIU	Ald	Lys ·	605	пур	IYI	Giu	
			JJJ					000					005				
	GCT	GAA	GCG	GCT	TTC	TTC	GCC	AAC	CTG	AAG	CTG	TCT	GAT	TTC	AAC	ATC	1872
	Ala	Glu	Ala	Ala	Phe	Phe	Ala	Asn	Leu	Lys	Leu	Ser	Asp	Phe	Asn	Ile	
30		610					615					620					
												GTA					1920
	625	Asp	Thr	Leu	GIA	630	GIY	GIY	Pne	GIY	635	Val	GIU	Leu	vaı	640	
35	025					630					635					040	
00	TTG	AAA	AGT	GAA	GAA	TCC	AAA	ACG	TTT	GCA	ATG	AAG	ATT	CTC	AAG	AAA	1968
												Lys					
	•	-			645		•			650		_			655	-	
40												ATC					2016
	Arg	His	Ile		_	Thr	Arg	Gln		Glu	His	Ile	Arg		Glu	Lys	
				660.					665					670			
	CAG	ΣΤС	ATG	CAG	GGG	ССТ	СУТ	TCC	СУТ	ጥጥር	מידמ	GTG	AGA	СТС	TAC	AGA	2064
45												Val					
			675		2			680					685		- 4	<b>-</b>	
																	,
	ACA	TTT	AAG	GAC	AGC	AAA	TAT	TTG	TAT	ATG	TTG	ATG	GAA	GCT	TGT	CTA	2112
	Thr		Lys	Asp	Ser	Lys	_	Leu	Tyr	Met	Leu	Met	Glu	Ala	Сув	Leu	
50		690					695					700					
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•																GAT	2160
	705	GTÀ	GIU	⊔∈u	ττb	710	**E	neu	ALG.	мър	715	Gly	3CI	PHE	GIU	720	
55	. 55					v											
	TCT	ACA	ACC	AGA	TTT	TAC	ACA	GCA	TGT	GTG	GTA	GAA	GCT	TTT	GCC	TAT	2208
																	. 2

									•	•							
	Ser	Thr	Thr	Arg	Phe 725	Tyr	Thr	Ala	Cys	Val 730	Val	Glu	Ala	Phe	Ala 735	Tyr	· ,
	CTG	CAT	TCC	AAA	GGA	ATC	ATT	TAC	AGG	GAC	CTC	AAG	CCA	GAA	AAT	CTC	2256
5		His															
				740					745					750			
•		CTA				_											2304
40	Ile	Leu	_	His	Arg	Gly	Tyr		Lys	Leu	Val	Asp		Gly	Phe	Ala	
10			755					760		٠			765			•	
	AAG	AAA	ATA	GGA	TTT	GGA	AAG	AAA	ACA	TGG	ACT	TTT	TGT	GGG	ACT	CCA	2352
	Lys	Lys	Ile	Gly	Phe	Gly	Lys	Lys	Thr	Trp	Thr	Phe	Cys	Gly	Thr	Pro	
		770					775					780					
15	a.a	TAT	CILL N	000	CCN	CAC	אתכ	N TO CO	CTC	אאמ	אאא	ccc	ርካጥ	GNC	א אווינה	TCA	2400
		Tyr															2400
	785	+ 7 -	vul	77.1.4		790			200		795	U				800	
20		GAC															2448
	Ala	Asp	Tyr	Trp		Leu	Gly	Ile	Leu		Tyr	Glu	Leu	Leu	Thr 815	GIY	
					805					810					015		
	AGC	CCA	CCT	TTC	TCA	GGC	CCA	GAT	CCT	ATG	AAA	ACC	TAT	AAC	ATC	ATA	2496
25	Ser	Pro	Pro	Phe	Ser	Gly	Pro	Asp	Pro	Met	Lys	Thr	Tyr	Asn	Ile	Ile	
				820	•				825			•		830			
	TTC	AGG	GGG	מידים	GAC	ልፕሮ	מדמ	CAA.	ተጥተ	CCA	DAG	DAG	АТТ	GCC	AAA	AAT	2544
•		Arg															
30		_	835		•			840				-	845		_		
																	0500
		GCT Ala															2592
	Ala	850	ASII	ьец	116	гур	БуБ 855	Leu	cys	AIG	App	860	FIO	Ser	GIU	ur a	
3 5			•														
		. GGG															2640
		Gly	Asn	Leu	Lys		Gly	Val	Lys	Asp		Gln	Lys	His	Lys		•
	865					870					875			٠		880	
40	ттт	GAG	GGC	TTT	AAC	TGG	GAA	GGC	TTA	AGA	AAA	GGT	ACC	TTG	ACA	CCT	2688
		Glu															
					885					890					895		
	~~~	200		<b>aa</b> .	» cm	amm	GG1	man	000	202	ar a	202	N CITT	א א מיי	en en en	CAC	2736
45																GAC Asp	2730
40	FIO	110	110	900	DCI	· · · ·	7114	001	905	****	1101			910			
																GGA	2784
50	Ser	Phe			Asp	Asn	Asp			Pro	Pro	Asp			Ser	Gly	
50			915					920					925				
	TGG	GAT	ATA	GAC	TTC	TAA											2802
	Trp	Asp	Ile	Asp	Phe				•								
		930								*							

274

## (2) INFORMATION FOR SEQ ID NO:135:

- (i) SEQUENCE CHARACTERISTICS:
  - (A) LENGTH: 933 amino acids
  - (B) TYPE: amino acid
  - (C) STRANDEDNESS: single
  - (D) TOPOLOGY: linear
- (ii) MOLECULE TYPE: protein
- 10 (v) FRAGMENT TYPE: internal

5

## (xi) SEQUENCE DESCRIPTION: SEQ ID NO:135:

15	Met 1	Val	Ser	Lys	Gly 5	Ġlu	Glu	Leu	Phe	Thr 10	Gly	Val	Val	Pro	Ile 15	Leu
				Asp 20		_			25		_			30		_
	Glu	Gly	Glu 35	Gly	Asp	Ala		Tyr 40	Gly	Lys	Leu [.]	Thr	Leu 45	Lys	Phe	Ile
20	-	50		Gly			55					60				
	65			Gly		70					75					80
25			_	Phe	85	-				90			-		95	•
	_			Phe 100					105		_			110		
			115	Glu				120					125			
30		130		Lys			135				_	140				
	145	_		Ser		150		_			155	_	_		_	160
35				Val	165					170					175	
				Ala 180			-		185					190		
40			195	Leu		_		200	_				205			
40		210		Pro			215					220				
•	225			Ala		230			_		235					240
45				Ser	245				_	250					255	
•				Glu 260	-				265	_		_	_	270		
<b>50</b>			275	Glu				280					285			
50		290		Glu			295	_				300				
	305				_	310					315		_			Arg 320
55		-	-	Gln	325					330				_	335	
	Asp	ьeu	ser	His	val	Tnr	Leu	Pro	Pne	Tyr	Pro	гÀа	ser	Pro	GID	ser

				340					345					350		
	Lys	Asp	Leu	Ile	Lys	Glu	Ala	Ile	Leu	Asp	Asn	Asp	Phe	Met	Lys	Asn
	_		355					360					365			
	Leu	Glu	Leu	Ser	Gln	Ile	Gln	Glu	Ile	Val	Asp	Cys	Met	Tyr	Pro	Val
5		370					375					380				
	Glu	Tyr	Gly	Lys	Asp	Ser	Cys	Ile	Ile	Lys	Glu	Gly	Asp	Val	Gly	Ser
	385	_	_	_		390					395					400
	Leu	Val	Tyr	Val	Met	Glu	Asp	Gly	Lys	Val	Glu	Val	Thr	Lys	Glu.	Gly
					405					410					415	
10	Val	Lys	Leu	Cys	Thr	Met	Gly	Pro	Gly	Lys	Val	Phe	Gly	Glu	Leu	Ala
				420					425					430		
•	Ile	Leu	Tyr	Asn	Cys	Thr	Arg	Thr	Ala	Thr	Val	Lys	Thr	Leu	Val	Asn
			435		•			440					445			
	Val	Lys	Leu	Trp	Ala	Ile	Asp	Arg	Gln	Cys	Phe	Gln	Thr	Ile	Met	Met
15		450					455					460				
	Arg	Thr	Gly	Leu	Ile	Lys	His	Thr	Glu	Tyr	Met	Glu	Phe	Leu	Lys	
	465			•		470					475				_	480
	Val	Pro	Thr	Phe		Ser	Leu	Pro	Glu		Ile	Leu	Ser	Lys		Ala
		_		_	485	_				490			_		495	_
20	Asp	Val	Leu		Glu	Thr	His	Tyr		Asņ	Gly	GIu	Tyr		TIE	Arg
		<b>~</b> 3		500	<b>a</b> 3	<b>3</b>	<b>(71)</b>	D)	505	T7.	<b>7</b> 1 -	0	T	510	mb	17.1
	GIn	GIA		Arg	GIY	Asp	Thr		Pne	116	Ile	ser		GIY	LIIL	Val
	2	1701	515	N	<u>ما.،</u>	7.00	Cow	520	Co.~	C1	7 cm	מאמ	525	Dho	T.611	λrα
25	Asn	530	Thr	Arg	GIU	Asp	535	PIO	ser	GIU	Asp	540	vaı	Pile	Deu	Arg
25	mh		<i>0</i> 1 <i>v</i>	Tara	G1v	A cm		Dha	Gly	Glu	Lys		T.em	Gln	Glv	Glu
	545	Deu	GLY	пåз	GIY	550	тър	FIIÇ	GIY	Giu	555	AIG	ДСИ	0111	O1,	560
		V21	Δτα	Thr	בומ		Val	Tle	Δla	Δla	Glu	Δla	Val	Thr	Cvs	
	Asp	VAI	Arg	1111	565	NO.	VAL	116		570	Olu	niu	***		575	
30	Val	Tle	Asp	Ara		Ser	Phe	Tivs	His		Ile	Glv	Glv	Leu		Asp
00	741			580	11.D.P	501		_,_	585			,	1	590		
	Val	Ser	Asn		Ala	Tvr	Glu	asp		Glu	Ala	Lys	Ala		Tyr	Glu
			595	2				600				•	605		•	
	Ala	Glu	Ala	Ala	Phe	Phe	Ala	Asn	Leu	Lys	Leu	Ser	Asp	Phe	Asn	Ile
35		610					615			-		620				
	Ile	Asp	Thr	Leu	Gly	Val	Gly	Gly	Phe	Gly	Arg	Val	Glu	Leu	Val	Gln
	625	_			-	630			•		635					640
	Leu	Lys	Ser	Glu	Glu	Ser	Lys	Thr	Phe	Ala	Met	Lys	Ile	Leu	Lys	Lys
					645					650					655	
40	Arg	His	Ile	Val	Asp	Thr	Arg	Gln	Gln	Glu	His	Ile	Arg	Ser	Glu	Lys
				660					665					670		
	Gln	Ile	Met	Gln	Gly	Ala	His		Asp	Phe	Ile	Val			Tyr	Arg
			675					680					685		_	_
	Thr		Lys	Asp	Ser	Lys		Leu	Tyr	Met	Leu		Glu	Ala	Cys	Leu
45		690	_		•		695					700	_	_,		_
		Gly	Glu	Leu	Trp		Ile	Leu	Arg	Asp	Arg	GIA	Ser	Phe	GIU	
	705			_	_,	710	_,		_		715	<b>~</b> 3		Dl	77-	720
	Ser	Thr	Thr	Arg		Tyr	Thr	Ala	Cys		Val	GIU	Ата	Pne		
<b>50</b>	_	'	_	_	725	-3.				730		T	D	<b>a</b> 1	735	
50	Leu	His	ser		GIY	TIE	Пе	Tyr			Leu	тув	PIO	750		neu
	-1-	<b>T</b>	N	740	7	<b>G3</b>	m	N 7 -	745		37-7	700	Dho			λla
	тте	neu		nis	Arg	сту	ıyr	760	ьys	neu	Val	Asp	765		FIIC	M. a
	I	Lare	755	G1 **	Dhe	GTv-	Tare		ጥኮታ	יאינו	Thr	Phe			Thr	Pro
55	nyg	дув 770	**6	- T	2116	GIY	775		****	++2		780		y		
55	Gl.		Val	בו ע	Pro	Glu	–		וופין	Agn	Lys			Asn	Tile	Ser
	GIU	- y -	- 44			O_Lu					_,_	1				

	785					790					795					800	
		Asp	Tyr	Trp	Ser 805		Gly	Ile		Met 810		Glu	Leu	Leu	Thr 815	Gly	
E	Ser	Pro	Pro			Gly	Pro	Asp			Lys	Thr	Tyr	Asn 830		Ile	
5	Leu	Arg	Gly 835	820 Ile	Asp	Met	Ile	Glu 840		Pro	Lys	Lys	Ile . 845		Lys	Asn	
	Ala	Ala 850	Asn	Leu	Ile	Lys	Lys 855		Cys	Arg	Asp	Asn 860	-	Ser	Glu	Arg	
10	Leu 865		Asn	Leu	Lys	Asn 870	-	Val	Lys	Asp	Ile 875		Lys	His	Lys	Trp 880	
		Glu	Gly	Phe	Asn		Glu	Gly	Leu	Arg		Gly	Thr	Leu	Thr		Ý.
•			_		885	-		_		890					895		
15	Pro	Ile	Ile	Pro	Ser	Val	Ala	Ser	Pro 905	Thr	Asp	Thr	Ser	Asn 910	Phe	Asp	
13	Ser	Phe	Pro	-	Asp	Asn	Asp	Glu		Pro	Pro	Asp	qaA		Ser	Gly	
			915					920					925				
	Trp	930	Ile	Asp	Phe		÷				·						
20																	
			(2)	INI	FORM	1OITA	1 FOI	R SE	DID	NO:	136:						
		(:	i) SI	EQUE	VCE (	CHAR	ACTE	RIST	cs:								
0.5						2799 cle:		_	airs					•		٠.	
25						ONES!			<b>e</b>			•					
						Y: 1:											
		(	ii) N	MOLE	TULE	түрі	i ci	AMC									
30			ix) l				J. C.	J1171									
			(2)	\ <b>&gt;</b> 77.1	412 / 1/1	737	7~44.	C									
						EY: (		_	eque	ice							
			(D)	OTI	HER :	INFO	RMAT:	ION:									
35			(D)	, 01.													
		(:	(D)		ENCE	DES	CRIP'	rion	: SE	Q ID	NO:	136:					
	ATG		xi) S	SEQU									GAG	AAG	ATC	GAG	48
		GGC		SEQUI	CGG	GAT	TTA	CAG	TAC	GCG	CTC	CAG				-	48
40		GGC	xi) s	SEQUI	CGG	GAT	TTA	CAG	TAC	GCG	CTC	CAG				-	48
40	Met 1	GGC Gly	xi) S ACC Thr	SEQUI TTG Leu	CGG Arg 5	GAT Asp	TTA Leu	CAG Gln	TAC Tyr	GCG Ala 10	CTC Leu	CAG Gln	Glu	Lys	Ile 15	-	48
40	Met 1 GAG	GGC Gly	ACC Thr	TTG Leu CAG	CGG Arg 5	GAT Asp	TTA Leu GCT	CAG Gln CTC	TAC Tyr ATC Ile	GCG Ala 10 GAC	CTC Leu GAG	CAG Gln CTG	Glu GAG	Lys CTG Leu	Ile 15 GAG	Glu	
	Met 1 GAG	GGC Gly	ACC Thr	SEQUI TTG Leu CAG	CGG Arg 5	GAT Asp	TTA Leu GCT	CAG Gln CTC	TAC Tyr	GCG Ala 10 GAC	CTC Leu GAG	CAG Gln CTG	Glu GAG	Lys CTG	Ile 15 GAG	Glu	
40	Met 1 GAG Glu	GGC Gly CTG Leu	ACC Thr AGG Arg	TTG Leu CAG Gln 20	CGG Arg 5 CGG Arg	GAT Asp GAT Asp	TTA Leu GCT Ala	CAG Gln CTC Leu	TAC Tyr ATC Ile 25	GCG Ala 10 GAC Asp	CTC Leu GAG Glu	CAG Gln CTG Leu	Glu GAG Glu	CTG Leu 30	Ile 15 GAG Glu	Glu	
	Met 1 GAG Glu GAT	GGC Gly CTG Leu	ACC Thr AGG Arg	TTG Leu CAG Gln 20	CGG Arg 5 CGG Arg	GAT Asp GAT Asp	TTA Leu GCT Ala	CAG Gln CTC Leu CAG Gln	TAC Tyr ATC Ile 25	GCG Ala 10 GAC Asp	CTC Leu GAG Glu	CAG Gln CTG Leu	GAG Glu GAG Glu	CTG Leu 30	Ile 15 GAG Glu GAC	Glu TTG Leu	96
	Met 1 GAG Glu GAT	GGC Gly CTG Leu	ACC Thr AGG Arg	TTG Leu CAG Gln 20	CGG Arg 5 CGG Arg	GAT Asp GAT Asp	TTA Leu GCT Ala	CAG Gln CTC Leu	TAC Tyr ATC Ile 25	GCG Ala 10 GAC Asp	CTC Leu GAG Glu	CAG Gln CTG Leu	Glu GAG Glu GAG	CTG Leu 30	Ile 15 GAG Glu GAC	Glu TTG Leu AAG	96
	Met 1 GAG Glu GAT Asp	GGC Gly CTG Leu CAG Gln	ACC Thr  AGG Arg  AAG Lys 35	TTG Leu CAG Gln 20 GAC Asp	CGG Arg 5 CGG Arg GAA Glu	GAT Asp GAT Asp CTG Leu	TTA Leu GCT Ala ATC Ile	CAG Gln CTC Leu CAG Gln 40	TAC Tyr ATC Ile 25 AAG Lys	GCG Ala 10 GAC Asp CTG Leu	CTC Leu GAG Glu CAG Gln	CAG Gln CTG Leu AAC Asn	GAG Glu GAG Glu 45 CAG	CTG Leu 30 CTG Leu	GAG Glu GAC Asp	TTG Leu AAG Lys	96
45	Met 1 GAG Glu GAT Asp	GGC Gly CTG Leu CAG Gln CGC Arg	ACC Thr  AGG Arg  AAG Lys 35	TTG Leu CAG Gln 20 GAC Asp	CGG Arg 5 CGG Arg GAA Glu	GAT Asp GAT Asp CTG Leu	TTA Leu GCT Ala ATC Ile CCA Pro	CAG Gln CTC Leu CAG Gln 40	TAC Tyr ATC Ile 25 AAG Lys	GCG Ala 10 GAC Asp CTG Leu	CTC Leu GAG Glu CAG Gln	CAG Gln CTG Leu AAC Asn	GAG Glu GAG Glu 45 CAG	CTG Leu 30 CTG Leu	GAG Glu GAC Asp	TTG Leu AAG Lys	96
45	Met 1 GAG Glu GAT Asp	GGC Gly CTG Leu CAG Gln	ACC Thr  AGG Arg  AAG Lys 35	TTG Leu CAG Gln 20 GAC Asp	CGG Arg 5 CGG Arg GAA Glu	GAT Asp GAT Asp CTG Leu	TTA Leu GCT Ala ATC Ile	CAG Gln CTC Leu CAG Gln 40	TAC Tyr ATC Ile 25 AAG Lys	GCG Ala 10 GAC Asp CTG Leu	CTC Leu GAG Glu CAG Gln	CAG Gln CTG Leu AAC Asn	GAG Glu GAG Glu 45 CAG	CTG Leu 30 CTG Leu	GAG Glu GAC Asp	TTG Leu AAG Lys	96
<b>45</b>	Met 1 GAG Glu GAT Asp TAC Tyr	GGC Gly CTG Leu CAG Gln CGC Arg 50	ACC Thr  AGG Arg  AAG Lys 35  TCG Ser	TTG Leu  CAG Gln 20 GAC Asp GTG Val	CGG Arg 5 CGG Arg GAA Glu ATC Ile	GAT Asp GAT Asp CTG Leu CGA Arg	TTA Leu GCT Ala ATC Ile CCA Pro 55	CAG Gln CTC Leu CAG Gln 40 GCC Ala	TAC Tyr ATC Ile 25 AAG Lys ACC Thr	GCG Ala 10 GAC Asp CTG Leu CAG Gln	CTC Leu GAG Glu CAG Gln CAG	CAG Gln CTG Leu AAC Asn GCG Ala 60 CGG	GAG Glu GAG Glu 45 CAG Gln	CTG Leu 30 CTG Leu AAG Lys	GAG Glu GAC Asp CAG Gln	TTG Leu AAG Lys AGC Ser	96
45	Met 1 GAG Glu GAT Asp TAC Tyr	GGC Gly CTG Leu CAG Gln CGC Arg 50	ACC Thr  AGG Arg  AAG Lys 35  TCG Ser	TTG Leu  CAG Gln 20 GAC Asp GTG Val	CGG Arg 5 CGG Arg GAA Glu ATC Ile	GAT Asp GAT Asp CTG Leu CGA Arg	TTA Leu GCT Ala ATC Ile CCA Pro 55	CAG Gln CTC Leu CAG Gln 40 GCC Ala	TAC Tyr ATC Ile 25 AAG Lys ACC Thr	GCG Ala 10 GAC Asp CTG Leu CAG Gln	CTC Leu GAG Glu CAG Gln CAG	CAG Gln CTG Leu AAC Asn GCG Ala 60 CGG	GAG Glu GAG Glu 45 CAG Gln	CTG Leu 30 CTG Leu AAG Lys	GAG Glu GAC Asp CAG Gln	TTG Leu AAG Lys AGC Ser	96 144 192

SUBSTITUTE SHEET (RULE 26)

	GAG Glu													28	38
5	TTC Phe													33	36
10	CTT Leu													3 (	34
15	ATT Ile 130													4:	32
20	 ATC    Ile													41	80
25	AAG Lys		•											5:	28
25	GGA Gly													5	76
30	GCG Ala										_	_		6:	24
35	CAA Gln 210													6	72
40	GAG Glu		Met	Phe	Leu				Thr					7	20
45	GAA Glu													7	68
	GAA Glu							Gln						8	16
50	TTT Phe						Val				Glu		TCA Ser	8	64
55		Glu				Leu				Lys			TGG	9	12

5				TTG Leu 310							960
3				GTA Val							1008
10				GGG Gly							1056
15				GCA Ala							1104
20				GAT Asp							1152
25				GAA Glu 390							1200
				ATT							1248
30			•	CGC Arg							1296
35				AGA Arg							1344
40				GAA Glu							1392
45				TCG Ser 470							1440
				GCT Ala		 				_	1488
50				CCA Pro		 			_		1536
55				TTT Phe							1584

5	ACA Thr 530										1632
	CTG Leu										1680
10	 CTA Leu										1728
15	CCT Pro									_	1776
20	 TTT Phe				-						1824
.25	TGC Cys 610										1872
	AAA Lys								Trp		1920
30	TTA Leu									GCA Ala	1968
35	CCC Pro										2016
40	CCA Pro		Asp								2064
45	 CCG Pro 690										2112
.0	GTG Val										2160
50	 AGC Ser							_		CTG Leu	2208
55						Lys			Trp	CCC Pro	2256

•					ACC Thr												2304
5										•							
					AAG												2352
	Pro	Asp 770	His	Met	Lys	Gln	His 775	Asp	Phe	Phe		Ser 780	Ala	Met	Pro	Glu	
10	GGC	TAC	GTC	CAG	GAG	CGC	ACC	ATC	TTC	TTC	AAG	GAC	GAC	GGC	AAC	TAC	2400
					Glu												•
	785					790					795					800	
	AAG	ACC	CGC	GCC	GAG	GTG	AAG	TTC	GAG	GGC	GAC	ACC	CTG	GTG	AAC	CGC	2448
15					Glu												
					805					810					815		
	ATC	GAG	CTG	AAG	GGC	ATC	GAC	TTC	AAG	GAG	GAC	GGC	AAC	ATC	CTG	GGG	2496
					Gly												
20				820					825			•		830			
	ראר	DAG	СТС	GAG	TAC	AAC	TAC	AAC	AGC	CAC	AAC	GTC	TAT	ATC	ATG	GCC	2544
					Tyr												•
		•	835	•	•		-	840					845				
25													7 ma	~~~	C D C	220	2592
					AAC Asn												2592
	Asp	850	GIII	пур	ASII	GIY	855	пуь	Val	ASII	1110	860					
		,															
30					AGC												2640
		Glu	Asp	Gly	Ser		Gln	Leu	Ala	Asp	875	ıyr	GIN	GIN	ABII	880	
	865					870					675						
																AGC	2688
35	Pro	Ile	Gly	Asp	Gly	Pro	Val	Leu	Leu			Asn	His	Tyr	Leu 895		
					885					890					693		
																ATG	2736
	Thr	Gln	Ser		Leu						Glu	Lys	Arg			Met	
40				900					905		٠			910			
	GTC	CTG	CTG	GAG	TTC	GTG	ACC	GCC	GCC	GGG	ATC	ACI	CTC	GGC	OTA:	GAC	2784
	Val	Leu	Leu	Glu	Phe	Val	Thr	Ala	Ala	Gly	Ile	Thr	Leu	Gly	Met	Asp	
•			915					920					925				
45			m= -		am= =							•					2799
•					GTAA												وراب
	GIU	Leu 930		пλр													
					,												
50			/2	\ TN	EODM	א דיי	N DO	ים פו	יה דד	NO.	127.	,					

#### (2) INFORMATION FOR SEQ ID NO:137:

- (i) SEQUENCE CHARACTERISTICS:
  - (A) LENGTH: 932 amino acids
  - (B) TYPE: amino acid

. 55

(C) STRANDEDNESS: single

(ii) MOLECULE TYPE: protein

(D) TOPOLOGY: linear

(v) FRAGMENT TYPE: internal

5

# (xi) SEQUENCE DESCRIPTION: SEQ ID NO:137:

	Met 1	Gly	Thr	Leu	Arg 5	Asp	Leu	Gln	Tyr	Ala 10	Leu	Gln	Glu	Lys	Ile 15	Glu
10	Glu	Leu	Arg	Gln 20	Arg	Asp	Ala	Leu	Ile 25	Asp	Glu	Leu	Glu	Leu 30	Glu	Leu
	-		Lys 35	_				40					45			
15	Tyr	Arg 50	Ser	Val	Ile	Arg	Pro 55	Ala	Thr	Gln	Gln	Ala 60	Gln	Lys	Gln	Ser
	Ala 65	Ser	Thr	Leu	Gln	Gly 70	Glu	Pro	Arg	Thr	Lys 75	Arg	Gln	Ala	Ile	Ser 80
			Pro		85	•	_			90					95	
20	•		Tyr	100					105					110		
			Asp 115					120					125			
25		130	Val	_			135				_	140	_			
	145		Lys		_	150		_			155					160
	_	-	Val		165					170					175	
30		_	Lys	180		_			185					190		
			Thr 195		_			200					205			
35		210	Cys				215					220				
	225		Tyr			230		_			235					240
			Glu		245	•				250					255	
40	_		Asn	260					265					270		
			275			-	_	280					285			Ser
45	•	290		_			295					300				Trp
	305			•		310					315					Val 320
					325					330					335	
50	-			340	_	_		_	345					350		Glu
			355					360					365			Ala
55		370					375			•		380				Gly
	Gly	Phe	Gly	Arg	Val	Glu	Leu	Val	Gln	Leu	Lys	Ser	Glu	Glu	Ser	Lys

	385					390					395					400
	Thr	Phe	Ala	Met	Lys 405	Ile	Leu	Lys	Lys	Arg 410	His	Ile	Val	Asp	Thr 415	
5			Glu	420		-			425					430		
			Phe 435			•		440					445		÷	
		450	Met				455	_		_	_	460		_		
10	465		Asp			470			-		475					480
			Val		485				_	490			_	_	495	
15	•		Asp	500	_				505			_		510		_
		_	Leu 515		_		_	520		_	-		525		_	_
20	_	530	Trp				535		,			540				
20	545		Asn			550					555	_	_			560
			Met Met		565					570					575	
25	_		Pro	580					585		-			590		
			595 Arg				•	600					605			
30		610	Asp				615	,	_			620				
30	625	_	Arg			630		_	-		635					640
	_		Thr		645					650					655	
35			Pro	660					665					670		
			675 Val					680					685			
40		690					695		_	_		700				Lys
	705					710			_		715			_		720 Leu
					725			•	_	730					735	
45				740		_			745	_				750		Pro
			755					760	_				765			Tyr
		770					775				_	780				Glu
50	785	-				790					795	_	_			Tyr 800
	_				805					810					815	Arg
55				820					825					830		Gly
	HIS	ьys	பeu	GIU	ryr	Asn	Tyr	Asn	ser	Hls	Asn	val	Tyr	тте	Met	Ala

			835					840					845					
	Asp	Lys 850	Gln	Lys	Asn	Gly	Ile 855	Lys	Val	Asn	Phe	Lys 860	Ile	Arg	His	Asn		
_		Glu	Asp	Gly	Ser		Gln	Leu	Ala	Asp		Tyr	Gln	Gln	Asn			
5	865 Pro	Ile	Gly	Asp	_	870 Pro	Val	Leu	Leu		875 Asp	Asn	His	Tyr		880 Ser		
	Thr	Gln	Ser	Ala 900	885 Leu	Ser	Lys	Asp		890 Asn	Glu	Lys	Arg	Asp 910	895 His	Met		
10	Val	Leu	Leu 915		Phe	Val	Thr	Ala 920	905 Ala	Gly	Ile	Thr	Leu 925		Met	Asp		
	Glu	Leu 930		Lys				,,,,		•			,,,					
15			(2)	INE	FORM	TION	1 FOI	R SEÇ	) ID	NO: 1	38:							
20		<b>(</b> )	(A) (B)	LENC TYPE	ETH:	2184 iclei	basic ac	RISTI se pa cid ingle	airs						•	,		
			(D)	TOPO	)LOG	7: li	inear											
25			x) I	OLEC FEATU	JRE:													
			(B)	LOC OTH	CATIO	on: 3	12		equer	ice		•						
30		(>	ci) S	EQUE	ENCE	DESC	CRIP	rion	: SE(	Q ID	NO:	138:						
0.5		GTG Val															48	
35		GAG Glu															96	
40		GGC															144	
45		ACC Thr 50															192	
50		ACC Thr			Val												240	
		CAC His															288	
55	CGC	ACC	ATC	TTC	TTC	AAG	GAC	GAC	GGC	AAC	TAC	AAG	ACC	CGC	GCC	GAG	336	283

	Arg	Thr	Ile	Phe 100	Phe	Lys	qaA	Asp	Gly 105	Asn	Tyr	Lys	Thr	Arg 110	Ala	Glu	
5		AAG Lys												Leu			384
10		GAC Asp 130															432
15		TAC Tyr									-						480
15		ATC Ile															528
20		CAG Gln															576
25		GTG Val															624
30		AAA Lys 210															672
35		ACC Thr															720
33		CTC Leu												Val			768
40	GGT Gly	TGG Trp															816
45		TTC Phe															864
50		CAG Gln 290														GTG Val	912
E.F.		CAG Gln															960
55	ATC	ATC	CGC	TGC	CTG	CAG	TGG	ACC	ACT	GTC	ATC	GAA	CGC	ACC	TTC	CAT	1008

																	•	
	Ile	Ile	Arg	Cys	Leu 325	Gln	Trp	Thr	Thr	Val 330	Ile	Glu	Arg	Thr	Phe 335	His		
5								GAG Glu									1056	
10	GTG Val	GCT Ala	GAC Asp 355	GGC	CTC Leu	AAG Lys	AAG Lys	CAG Gln 360	GAG Glu	GAG Glu	GAG Glu	GAG Glu	ATG Met 365	GAC Asp	TTC Phe	CGG Arg	1104	
	TCG Ser	GGC Gly 370	TCA	CCC Pro	AGT Ser	GAC Asp	AAC Asn 375	TCA Ser	GGG Gly	GCT Ala	GAA Glu	GAG Glu 380	ATG Met	GAG Glu	GTG Val	TCC Ser	1152	
15	Leu	GCC				His	CGC	GTG Val				GAG					1200	
20					Lys			TTC Phe		Lys	GTG				Lys	GAG	1248	
25								GCC Ala						Lys			1296	-
					GAC			GCC Ala									1344	
30	CTG	CAG	435 AAC	TCC	AGG	CAC	ccc	440 TTC Phe	CTC	ACA	GCC	CTG	445 AAG	TAC	TCT	TTC	1392	
35	CAG	450 ACC	CAC	GAC	CGC	CTC	455 TGC	TTT	GTC	ATG	GAG	460 TAC	GCC	AAC	GGG	GGC	1440	
40	465					470					475					Gly 480	1488	
	Glu	Leu	Phe	Phe	His 485	Leu	Ser	Arg	Glu	Arg 490	Val	Phe	e Ser	Glu	Asp 495	Arg	1526	
45	Ala	Arg	Phe	Tyr 500	Gly	Ala	Glu	Ile	Val 505	Ser	· Ala	Leu	ı Asp	Tyr 510	Leu	CAC His	1536	
50	TCG Ser	GAG Glu	AAG Lys 515	Asn	GTG Val	GTG Val	TAC Tyr	CGG Arg 520	Asp	CTC Lev	AAG Lys	CTO	G GAG 1 Glv 525	Asr	CTC Lev	ATG Met	1584	
			Lys					Lys					e Gly			C AAG S Lys	1632	
55	GAG	GGG	ATC	: AAG	GAC	GGT	r GCC	C ACC	ATC	OAA, E	G ACC	C TT	r TG0	C GG(	C AC	A CCT	1680	285

	Glu 545	Gly	Ile	Lys	Asp	Gly 550	Ala	Thr	Met	Lys	Thr 555	Phe	Cys	Gly	Thr	Pro 560	
5						GAG Glu											1728
10						CTG Leu											1776
						AAC Asn										ATC Ile	1824
15						CGC Arg											1872
20						CTG Leu 630											1920
25						GCC Ala											1968
30						CAC His											2016
35						TCG Ser										_	2064
00			_			ATC Ile											2112
40						AGC Ser 710											2160
45						ACG Thr		TGA									2184
50						ATIO				NO:	139:						
		(:	(A) (B)	LEN	GTH: E: a	CHAR 727 mino DNES	ami:	no a d	cids								
55						Y: 1											

(ii) MOLECULE TYPE: protein (v) FRAGMENT TYPE: internal

#### (xi) SEQUENCE DESCRIPTION: SEQ ID NO:139:

5 Met Val Ser Lys Gly Glu Glu Leu Phe Thr Gly Val Val Pro Ile Leu Val Glu Leu Asp Gly Asp Val Asn Gly His Lys Phe Ser Val Ser Gly 25 Glu Gly Glu Gly Asp Ala Thr Tyr Gly Lys Leu Thr Leu Lys Phe Ile 10 Cys Thr Thr Gly Lys Leu Pro Val Pro Trp Pro Thr Leu Val Thr Thr Leu Thr Tyr Gly Val Gln Cys Phe Ser Arg Tyr Pro Asp His Met Lys 15 70 Gln His Asp Phe Phe Lys Ser Ala Met Pro Glu Gly Tyr Val Gln Glu Arg Thr Ile Phe Phe Lys Asp Asp Gly Asn Tyr Lys Thr Arg Ala Glu 105 Val Lys Phe Glu Gly Asp Thr Leu Val Asn Arg Ile Glu Leu Lys Gly 20 Ile Asp Phe Lys Glu Asp Gly Asn Ile Leu Gly His Lys Leu Glu Tyr Asn Tyr Asn Ser His Asn Val Tyr Ile Met Ala Asp Lys Gln Lys Asn 25 150 155 Gly Ile Lys Val Asn Phe Lys Ile Arg His Asn Ile Glu Asp Gly Ser 170 Val Gln Leu Ala Asp His Tyr Gln Gln Asn Thr Pro Ile Gly Asp Gly 185 Pro Val Leu Leu Pro Asp Asn His Tyr Leu Ser Thr Gln Ser Ala Leu 30 200 Ser Lys Asp Pro Asn Glu Lys Arg Asp His Met Val Leu Leu Glu Phe 215 Val Thr Ala Ala Gly Ile Thr Leu Gly Met Asp Glu Leu Tyr Lys Ser 35 Gly Leu Arg Ser Arg Gly Thr Met Ser Asp Val Ala Ile Val Lys Glu 245 250 Gly Trp Leu His Lys Arg Gly Glu Tyr Ile Lys Thr Trp Arg Pro Arg 265 Tyr Phe Leu Leu Lys Asn Asp Gly Thr Phe Ile Gly Tyr Lys Glu Arg 40 280 Pro Gln Asp Val Asp Gln Arg Glu Ala Pro Leu Asn Asn Phe Ser Val Ala Gln Cys Gln Leu Met Lys Thr Glu Arg Pro Arg Pro Asn Thr Phe 45 Ile Ile Arg Cys Leu Gln Trp Thr Thr Val Ile Glu Arg Thr Phe His 330 325 Val Glu Thr Pro Glu Glu Arg Glu Glu Trp Thr Thr Ala Ile Gln Thr 345 Val Ala Asp Gly Leu Lys Lys Gln Glu Glu Glu Met Asp Phe Arg 50 360 Ser Gly Ser Pro Ser Asp Asn Ser Gly Ala Glu Glu Met Glu Val Ser 380 Leu Ala Lys Pro Lys His Arg Val Thr Met Asn Glu Phe Glu Tyr Leu 55 Lys Leu Leu Gly Lys Gly Thr Phe Gly Lys Val Ile Leu Val Lys Glu

					405					410					415	
	Lys	Ala	Thr	Gly 420	Arg	Tyr	Tyr	Ala	Met 425	Lys	Ile	Leu	ГЛЗ	Lys 430	Glu	Val
	Ile	Val	Ala		Asp	Glu	Val	Ala	His	Thr	Leu	Thr	Glu	Asn	Arg	Val
5			435					440					445			
	Leu	Gln 450	Asn	Ser	Arg	His	Pro 455	Phe	Leu	Thr	Ala	Leu 460	Lys	Tyr	Ser	Phe
	Gln	Thr	His	Asp	Arg	Leu	Cys	Phe	Val	Met	Glu	Tyr	Ala	Asn	Gly	Gly
	465					470					475					480
10	Glu	Leu	Phe	Phe	His 485	Leu	Ser	Arg	Glu	Arg 490	Val	Phe	Ser	Glu	Asp 495	
•	Ala	Arg	Phe	Tyr 500	Gly	Ala	Glu	Ile	Val 505		Ala	Leu	qaA	Tyr 510	Leu	His
	Ser	Glu	Lys	Asn	Val	Val	Tyr	Arg	Asp	Leu	Lys	Leu	Glu	Asn	Leu	Met
15			515				-	520	_				525			
	Leu	Asp 530	Lys	Asp	Gly	His	Ile 535	Lys	Ile	Thr	Asp	Phe 540	Gly	Leu	Cys	Lys
	Glu	Gly	Ile	Lys	Asp	Gly	Ala	Thr	Met	Lys	Thr	Phe	Cys	Gly	Thr	Pro
	545	-		_		550				_	555				•	560
20	Glu	Tyr	Leu	Ala	Pro 565	Glu	Val	Leu	Glu	Asp 570	Asn	Asp	Tyr	Gly	Arg 575	Ala
	Val	Asp	Trp	Trp	Gly	Leu	Gly	Val	Val	Met	Tyr	Glu	Met	Met	Cys	Gly
			•	580	-				585					590		
25	Arg	Leu	Pro 595	Phe	Tyr	Asn	Gln	Asp 600	His	Glu	Lys	Leu	Phe 605	Glu	Leu	Ile
		610					615					620		Glu		
	Ser	Leu	Leu	Ser	Gly	Leu	Leu	Lys	Lys	Asp	Pro	Lys	Gln	Arg	Leu	Gly
	625					630					635					640
30	Gly	Gly	Ser	Glu	Asp 645	Ala	Lys	Glu	Ile	Met 650	Gln	His	Arg	Phe	Phe 655	Ala
	Gly	Ile	Val	Trp 660	Gln	His	Val	Tyr	Glu 665		Lys	Leu	Ser	Pro 670	Pro	Phe
0.5	Lys	Pro		Val	Thr	Ser	Glu			Thr	Arg	Tyr		Asp	Glu	Glu
35		_,	675	~ 1		-1-	·m1	680		D		N	685	7 ~~	7 ~~	Co~
		690					695					700		Asp		
			Cys	Val	Asp			Arg	Arg	Pro			Pro	Gin	Phe	Ser
	705					710					715				•	720
40	Tyr	Ser	Ala	Ser	Ser 725		Ala									

## (2) INFORMATION FOR SEQ ID NO:140:

45 (i) SEQUENCE CHARACTERISTICS:

- (A) LENGTH: 2394 base pairs
- (B) TYPE: nucleic acid
- (C) STRANDEDNESS: single
- (D) TOPOLOGY: linear

50 (ii) MOLECULE TYPE: cDNA

(ix) FEATURE:

- (A) NAME/KEY: Coding Sequence
- (B) LOCATION: 1...2391
  - (D) OTHER INFORMATION:

## (xi) SEQUENCE DESCRIPTION: SEQ ID NO:140:

		~~ ~					-					-				~~~	4.0	
5				CTG Leu													48	Ď
10		_		TAT Tyr 20							_						96	
45				TAC Tyr													.144	
15				ACA Thr													192	
20				GGA Gly													240	
25				CGG Arg													288	
30				TAT Tyr 100													336	
35				CTG Leu											_	_	3,84	
33				CAG Gln													432	
40				CAG Gln													480	
45				ACA Thr								-					528	
50				CCT Pro 180													576	
EE				ATC Ile												GGT Gly	624	
55	GGG	gat	GAG	ATC	TTC	CTA	CTG	TGT	GAC	AAG	GTG	CAG	AAA	GAG	GAC	ATT	672	289

	Gly	Asp 210	Glu	Ile	Phe	Leu	Leu 215	Cys	Asp	Lys	Val	Gln 220	Lys	Glu	Asp	Ile		
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20						CTG Leu											· 1584	
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				Phe												2200
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25				GAC Asp											AAA Lys	2304
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35				ATC Ile								Tyr				2394
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45		(	v) F	MOLE	ENT	TYPE	: in	tern	al			141				
50				SEQU Leu						Pro				Ala	n Ala	
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55			35					40					45		o Gly e Asn	-
																29

WO 98/45704 PCT/DK98/00145

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15					165	, -	_			170	_			Arg	175	
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20	· -	210					215			-		220		Glu		
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35		•			325					330					335	Thr
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50			435					440					445			Thr
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	465					470					475					480 Tyr
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40
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              (A) LENGTH: 2394 base pairs
              (B) TYPE: nucleic acid
              (C) STRANDEDNESS: single
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              (D) TOPOLOGY: linear
            (ii) MOLECULE TYPE: cDNA
            (ix) FEATURE:
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               (B) LOCATION: 1...2391
               (D) OTHER INFORMATION:
            (xi) SEQUENCE DESCRIPTION: SEQ ID NO:142:
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                                                                              294
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45	Met									EQ II e Thi		•		l Pro	o Ile	e Leu		
	1 Va	l Glı	ı Lev	ı Asp 20	5 Gl ₃	/ Asp	Val	l Ası	1 Gly 25	10 y His	s Ly	s Phe	e Se	r Va. 30		r Gly		
50			35	ı Gly				40	r Gl				45	ı Ly	s Ph	e Ile		
	_	50					55					60				r Thr t Lys		
55	65		_			70					75					80 n Glu		
																		29

					85					90					95	
	Arg	Thr		Phe 100	Phe	Lys	Asp		Gly 105	Asn	Tyr	Lys		Arg 110	Ala	Glu
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<b>.</b>	Ile	Asp 130		Lys	Glu	Asp	Gly 135		Ile	Leu	Gly	His 140	Lys	Leu	Glu	Tyr
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30		Leu			325					330			•		335	
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	Pro	o Met			e Glr	туз	r Le			p Th	r As	p As	p Ar	g Hi	s Ar	g Ile

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#### CLAIMS

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- 1. A method for extracting quantitative information relating to an influence on a cellular response, the method comprising recording variation, caused by the influence on a mechanically intact living cell or mechanically intact living cells, in spatially distributed light emitted from a luminophore, the luminophore being present in the cell or cells and being capable of being redistributed in a manner which is related with the degree of the influence, and/or of being modulated by a component which is capable of being redistributed in a manner which is related to the degree of the influence, the association resulting in a modulation of the luminescence characteristics of the luminophore, and processing the recorded variation in the spatially distributed light to provide quantitative information correlating the spatial distribution to the degree of the influence on the cellular response.
- 2. A method according to claim 1, as used for extracting quantitative information relating to an influence on an intracellular pathway involving redistribution of at least one component associated with the pathway, or part thereof, the method comprising recording the result of the influence on mechanically intact living cell or cells, as manifested in spatially distributed light emitted from a luminophore which is present in the cell or cells and which is capable of being redistributed, by modulation of the pathway, in a manner which is related to the redistribution of the at least one component of the intracellular pathway, processing the recorded result to provide quantitative information about the spatially distributed light and correlating the quantitative information to the degree of the influence on the intracellular pathway.
- 3. A method according to claim 1 or 2, wherein the quantitative information which is indicative of the degree of the cellular response to the influence or the result of the influence on the intracellular pathway is extracted from the recording or recordings according to a predetermined calibration based on responses or results, recorded in the same manner, to known degrees of a relevant specific influence.
- 4. A method according to any of the preceding claims, wherein the influence is contact between the mechanically intact living cell or the group of mechanically intact living cells with a

chemical substance and/or incubation of the mechanically intact living cell or the group of mechanically intact living cells with a chemical substance.

- 5. A method according to claim 4 wherein the substance is a substance whose effect on an intracellular pathway is to be determined.
- 6. A method according to any of the preceding claims, wherein the recording is made at a single point in time after the application of the influence.
- 7. A method according to any of claims 1-5, wherein the recording is made at two points in time, one point being before, and the other point being after the application of the influence.
  - 8. A method according to any of claims 1-5, wherein the recording is performed at a series of points in time, in which the application of the influence occurs at some time after the first time point in the series of recordings, the recording being performed, e.g., with a predetermined time spacing of from 0.1 seconds to 1 hour, preferably from 1 to 60 seconds, more preferably from 1 to 30 seconds, in particular from 1 to 10 seconds, over a time span of from 1 second to 12 hours, such as from 10 seconds to 12 hours, e.g., from 10 seconds to one hour, such as from 60 seconds to 30 minutes or 20 minutes.

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- 9. A method according to any of claims 1-7, wherein the cell or cells is/are fixed at a point in time after the application of the influence at which the response has been predetermined to be significant, and the recording is made at an arbitrary later time.
- 10. A method according to any of the preceding claims, wherein the luminophore is a luminophore which is capable of being redistributed in a manner which is physiologically relevant to the degree of the influence.

- 11. A method according to any of the preceding claims, wherein the luminophore is a luminophore which is capable of associating with a component which is capable of being redistributed in manner which is physiologically relevant to the degree of the influence.
- 12. A method according to any of the preceding claims, wherein the luminophore is a luminophore which is capable of being redistributed in a manner which is experimentally determined to be correlated to the degree of the influence.
- 13. A method according to any of the preceding claims, wherein the luminophore is a luminophore which is capable of being redistributed, by modulation of the intracellular pathway, in substantially the same manner as the at least one component of the intracellular pathway.
- 14. A method according to any of claims 1-13, wherein the luminophore is a luminophore which is capable of being quenched upon spatial association with a component which is redistributed by modulation of the pathway, the quenching being measured as a decrease in the intensity of the luminescence.
- 15. A method according to any of claims 1-13, wherein the variation or result with respect to the spatially distributed light emitted by the luminophore is detected by a change in the resonance energy transfer between the luminophore and another luminescent entity capable of delivering energy to the luminophore, each of which has been selected or engineered to become part of, bound to or associated with particular components of the intracellular pathway, and one of which undergoes redistribution in response to the influence, thereby changing the amount of resonance energy transfer, the change in the resonance energy transfer being measured as a change in the intensity of emission from the luminophore.
  - 16. A method according to claim 15, wherein the change in the intensity of the emission from the luminophore is sensed by a single channel photodetector which responds only to the average intensity of the luminophore in a non-spatially resolved fashion

17. A method according to any of claims 1-16, wherein the property of the light being recorded is intensity, fluorescence lifetime, polarization, wavelength shift, or other property which is modulated as a result of the underlying cellular response.

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- 18. A method according to any of claims 1-15 or 17, wherein the recording of the spatially distributed light is performed using a recording system which records the spatial distribution of a recordable property of the light in the form of an ordered array of values.
- 19. A method according to claim 18, wherein the recording of the spatial distribution of the recordable property of the light is performed using a charge transfer device such as a CCD array or a vacuum tube device such as a vidicon tube.
  - 20. A method according to any of the preceding claims, wherein the light to be measured passes through a filter which selects the desired component of the light to be measured and rejects other components.
  - 21. A method according to any of the preceding claims, wherein the recording of the spatial distribution of the recordable property of light is performed by fluorescence microscopy.

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- 22. A method according to any of the preceding claims, wherein the recording of the variation or result with respect to light emitted from the luminophore is performed by recording the spatially distributed light as one or more digital images, and the processing of the recorded variation to reduce it to one or more numbers representative of the degree of redistribution comprises a digital image processing procedure or combination of digital image processing procedures.
- 23. A method according to any of claims 2-22, wherein the intracellular pathway is an intracellular signalling pathway.

- 24. A method according to any of the preceding claims, wherein the luminophore is a fluorophore.
- 5 25. A method according to any of the preceding claims wherein the luminophore is a polypeptide encoded by and expressed from a nucleotide sequence harboured in the cell or cells.
- 26. A method according to any of the preceding claims, wherein the luminophore is a hybrid polypeptide comprising a fusion of at least a portion of each of two polypeptides one of which comprises a luminescent polypeptide and the other one of which comprises a biologically active polypeptide, as defined herein.
- 27. A method according to claim 26, wherein the luminescent polypeptide is a GFP as defined herein.
  - 28. A method according to claim 27 wherein the GFP is selected from the group consisting of green fluorescent proteins having the F64L mutation as defined herein.
- 29. A method according to claim 28 wherein the GFP is a GFP variant selected from the group consisting of F64L-GFP, F64L-Y66H-GFP, F64L-S65T-GFP, and EGFP.
  - 30. A method according to any of the previous claims for detecting intracellular translocation of a biologically active polypeptide affecting intracellular processes upon activation, the method comprising
    - a) culturing one or more cells containing a nucleotide sequence coding for a hybrid polypeptide comprising a GFP which is N- or C-terminally tagged, optionally through a linker, to a biologically active polypeptide under conditions permitting expression of the nucleotide sequence,

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- b) modulating the activity of the biologically active polypeptide by incubating the cell or cells with a substance having biological activity and
- c) measuring the fluorescence produced by the incubated cell or cells and determining the result or variation with respect to the fluorescence, such result or variation being indicative of the translocation of a biologically active polypeptide in said cell.
- 31. A method according to claim 30, wherein the nucleotide sequence is a DNA sequence.
- 32. A method according to claim 30 or 31, wherein the modulation is an activation.
- 33. A method according to claim 30 or 31, wherein the modulation is a deactivation.
- 34. A method according to any of claims 30-33 wherein the fluorescence of the cell or cells is measured prior to the modulation, and the result or variation determined in step (c) is a change in fluorescence compared to the fluorescence measured prior to the modulation.
  - 35. A method according to any of claims 30-34, wherein the intracellular processes are intracellular signalling pathways.
- 36. A method according to claim 34, wherein the change in fluorescence measured in step(c) comprises determining a change in the spatial distribution of the fluorescence.
  - 37. A method according to any of the preceding claims wherein the mechanically intact living cell or cells is/are a mammalian cell/mammalian cells which, during the time peroid over which the influence is observed, is/are incubated at a temperature of 30°C or above, preferably at a temperature of from 32°C to 39°C, more preferably at a temperature of from 35°C to 38°C, and most preferably at a temperature of about 37°C.

- 38. A method according to any of the preceding claims, wherein the at least one mechanically intact living cell is part of a matrix of identical or non-identical cells.
- 39. A method according to any of claims 1-36 and 38, wherein the cell or cells is/are selected from the group consisting of fungal cells, such as a yeast cell; invertebrate cells including insect cells; and vertebrate cells, such as mammalian cells.
  - 40. A nucleic acid construct coding for a fusion polypeptide comprising a biologically active polypeptide that is a component of an intracellular signalling pathway, or a part thereof, and a GFP, with the proviso that the construct is not a construct coding for a fusion polypeptide in which the biologically active polypeptide is selected from the group consisting of PKC-alpha, PKC-gamma, and PKC-epsilon.
- 41. A nucleic acid construct coding for a fusion polypeptide comprising a biologically active polypeptide that is a component of an intracellular signalling pathway, or a part thereof, and an F64L mutant of GFP.
  - 42. A nucleic acid construct according to claim 40 or 41, wherein the biologically active polypeptide is a protein kinase or a phosphatase.

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- 43. A nucleic acid construct according to any of claims 40-42 wherein the GFP is N- or C-terminally tagged, optionally via a peptide linker, to the biologically active polypeptide or part thereof.
- 44. A nucleic acid construct according to any of claims 40, 41 and 43, wherein the biologically active polypeptide is a transcription factor or a part thereof which changes cellular localisation upon activation.

- 45. A nucleic acid construct according to any of claims 40, 41 and 43, wherein the biologically active polypeptide is a protein, or a part thereof, which is associated with the cytoskeletal network and which changes cellular localisation upon activation.
- 46. A nucleic acid construct according to any of claims 40-43, wherein the biologically active polypeptide is a protein kinase or a part thereof which changes cellular localisation upon activation.
- 47. A nucleic acid construct according to claim 46, wherein the protein kinase is a serine/threonine protein kinase or a part thereof capable of changing intracellular localisation upon activation.
  - 48. A nucleic acid construct according to claim 46, wherein the protein kinase is a tyrosine protein kinase or a part thereof capable of changing intracellular localisation upon activation.
  - 49. A nucleic acid construct according to claim 46, wherein the protein kinase is a phospholipid-dependent serine/threonine protein kinase or a part thereof capable of changing intracellular localisation upon activation.
- 50. A nucleic acid construct according to claim 46, wherein the protein kinase is a cAMP-dependent protein kinase or a part thereof capable of changing cellular localisation upon activation.
- 51. A nucleic acid construct according to claim 50 which codes for a PKAc-F64L-S65T-GFP fusion.
  - 52. A nucleic acid construct according to claim 46, wherein the protein kinase is a cGMP-dependent protein kinase or a part thereof capable of changing cellular localisation upon activation.

53. A nucleic acid construct according to claim 46, wherein the protein kinase is a calmodulin-dependent serine/threonine protein kinase or a part thereof capable of changing cellular localisation upon activation.

- 54. A nucleic acid construct according to claim 46, wherein the protein kinase is a mitogenactivated serine/threonine protein kinase or a part thereof capable of changing cellular localisation upon activation.
- 55. A nucleic acid construct according to claim 54, which codes for an ERK1-F64L-S65T-GFP fusion.
  - 56. A nucleic acid construct according to claim 54, which codes for an EGFP-ERK1 fusion.
- 57. A nucleic acid construct according to claim 46, wherein the protein kinase is a cyclindependent serine/threonine protein kinase or a part thereof capable of changing cellular localisation upon activation.
- 58. A nucleic acid construct according to claim 42 or 43, wherein the biologically active polypeptide is a protein phosphatase or a part thereof capable of changing cellular localisation upon activation.
  - 59. A nucleic acid construct according to any of claims 40-58 which is a DNA construct.
- 25 60. A nucleic acid construct according to any of claims 40-59 wherein the gene encoding GFP is derived from Aequorea victoria.
  - 61. A nucleic acid construct according to claim 60 in which the gene encoding GFP is the gene encoding EGFP as defined herein.

62. A nucleic acid construct according to claim 60 in which the gene encoding a GFP is a gene encoding a GFP variant selected from F64L-GFP, F64L-Y66H-GFP and F64L-S65T-GFP.

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- 63. A DNA construct according to claim 59 and 61 or, where applicable, 62, which is a construct as identified by any of the DNA sequences shown in SEQ ID NO: 38, 40, 42, 44, 46, 48, 50, 52, 54, 56, 58, 60, 62, 64, 66, 68, 70, 72, 74, 76, 78, 108, 110, 112, 114, 116, 118, 120, 122, 124, 126, 128, 130, 132, 134, 136, 138, 140, and 142, or is a variant thereof capable of encoding the same fusion polypeptide or a fusion polypeptide which is biologically equivalent thereto, as defined herein.
- 64. A cell containing a nucleic acid construct according to any of claims 40-63 and capable of expressing the sequence encoded by the construct.

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- 65. A cell according to claim 64, which is a eukaryotic cell.
- 66. A cell according to claim 64, which is selected from the group consisting of fungal cells, such as yeast cells; invertebrate cells, including insect cells, and vertebrate cells, such as mammalian cells.
- 67. A cell according to claim 66, which is a mammalian cell.
- 68. An organism carrying in at least one of its component cells a nucleic acid sequence as contained in the constructs according to any of claims 40-59, said cell being capable of expressing said nucleic acid sequence.
  - 69. An organism according to claim 68 which is selected from the group consisting of unicellular and multicellular organisms, such as a mammal.

- 70. A fluorescent probe comprising a GFP which is N- or C-terminally tagged, optionally via a peptide linker, to a biologically active polypeptide or a part or a subunit thereof which is a component of a intracellular signalling pathway as defined herein, the probe being a probe which is encoded by the nucleic acid construct according to any of claims 40-59.
- 71. A method according to any of claims 1-39, wherein the luminophore is a fusion polypeptide as encoded by the nucleic acid construct according to any of claims 40-63.
- 72. A method according to any of claims 1-39 or 71 in which the method of the invention is used in a screening program as defined herein.
  - 73. An apparatus for measuring the distribution of fluorescence in at least one cell, and thereby any change in the distribution of fluorescence in at least one cell, which includes the following component parts: (a) a light source, (b) a means for selecting the wavelength(s) of light from the source which will excite the fluorescence of the protein, (c) a means for rapidly blocking or pass ing the excitation light into the rest of the system, (d) a series of optical elements for conveying the excitation light to the specimen, collecting the emitted fluorescence in a spatially resolved fashion, and forming an image from this fluorescence, (e) a bench or stand which holds the container of the cells being measured in a predetermined geometry with respect to the series of optical elements, (f) a detector to record the spatially resolved fluorescence in the form of an image, (g) a computer or electronic system and associated software to acquire and store the recorded images, and to compute the degree of redistribution from the recorded images.

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- 74. An apparatus according to claim 73 in which some or all of the system is automated.
- 75. An apparatus according to claim 73 in which components d and e comprise a fluorescence microscope.

- 76. An apparatus according to claim 73 in which component f is a CCD camera.
- 77. An apparatus according to claim 73 in which the image is formed and recorded by an optical scanning system.

- 78. An apparatus according to claim 73 in which a liquid addition system is used to add a known or unknown compound to any or all of the cells in the cell holder at a time determined in advance.
- 79. An apparatus according to claim 78 in which the liquid addition system is under the control of the computer or electronic system.
  - 80. A method according to any of claims 1-79 wherein the method is a screening program for the identification of a biologically active substance as defined herein that directly or indirectly affects an intracellular signalling pathway and is potentially useful as a medicament, wherein the result of the individual measurement of each substance being screened which indicates its potential biological activity is based on measurement of the redistribution of spatially resolved luminescence in living cells and which undergoes a change in distribution upon activation of an intracellular signalling pathway.

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- 81 A method according to any of claims 1-79 wherein the method is a screening program for the identification of a biologically toxic substance as defined herein that exerts its toxic effect by interfering with an intracellular signalling pathway, wherein the result of the individual measurement of each substance being screened which indicates its potential biologically toxic activity is based on measurement of the redistribution of said fluorescent probe in living cells and which undergoes a change in distribution upon activation of an intracellular signalling pathway.
- 82. A method according to any of claims 1-80 wherein a fluorescent probe is used in back-30 tracking of signal transduction pathways as defined herein.

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- 83. A method of treating a condition or disease related to the intracellular function of a protein kinase comprising administering to a patient suffering from said condition or disease an effective amount of a compound which has been discovered by any method according to the invention.
- 84. A compound that modulates a component of an intracellular pathway as defined herein, as determined by a method according to the method of the invention.
- 85. A medical composition comprising a therapeutic amount of a compound identified according the method of the invention.
  - 86. A method of selectively treating a patient suffering from an ailment which responds to medical treatment comprising obtaining a primary cell or cells from said patient, transfecting the cell or cells with at least one DNA sequence encoding a fluorescent probe according to the invention, culturing the cell or cells under conditions permitting the expression of said probes and exposing it to an array of medicaments suspected of being capable of alleviating said ailment, then comparing changes in fluorescence patterns or redistribution patterns of the fluorescent probes in the intact living cell or cells to detect the cellular response to the specific medicaments (obtaining a cellular action profile), then selecting a medicament(s) based on desired activity and acceptable level of side effects and administering an effective amount of said medicament(s) to said patient.
- 87. A method according to any of claims 1-80 of identifying a drug target among the group of biologically active polypeptides which are components of intracellular signalling pathways.

Fig 1

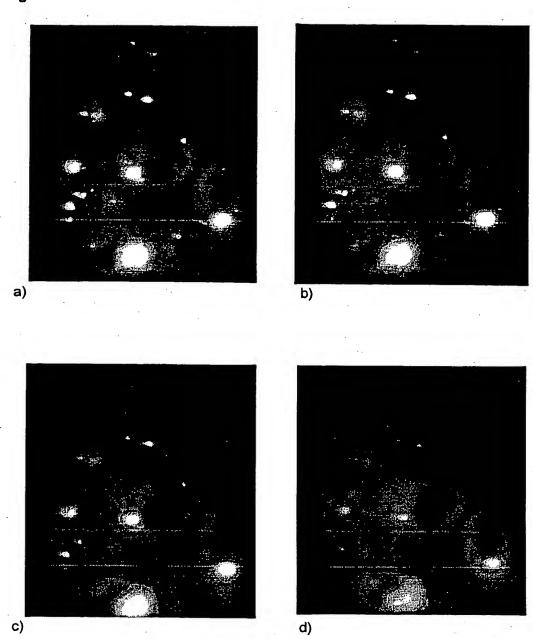


Fig 2

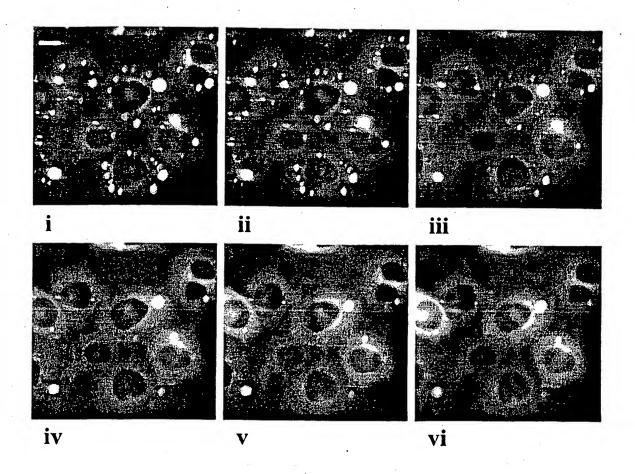
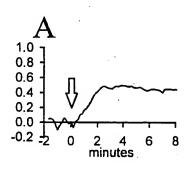
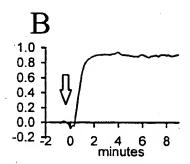
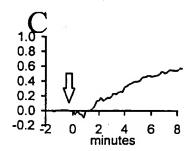
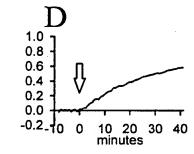


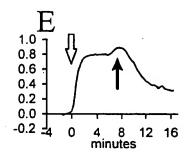
Fig 3

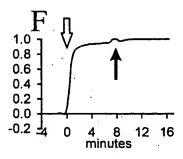


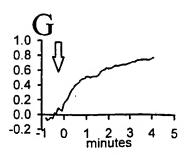












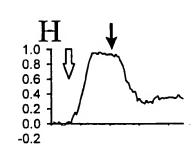
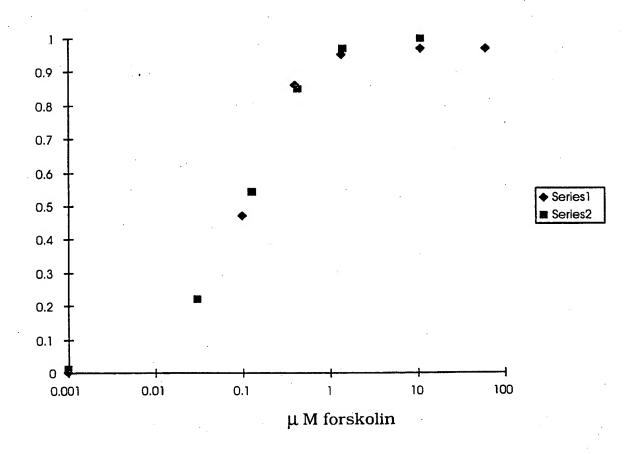


Fig 4



5/12

Fig 5

[forskolin]µM	$t_{1/2\text{max}}/s$	t _{max} /s
1	115±21	310±31
10	69±14	224±47
50	47±10	125±28

Fig 6

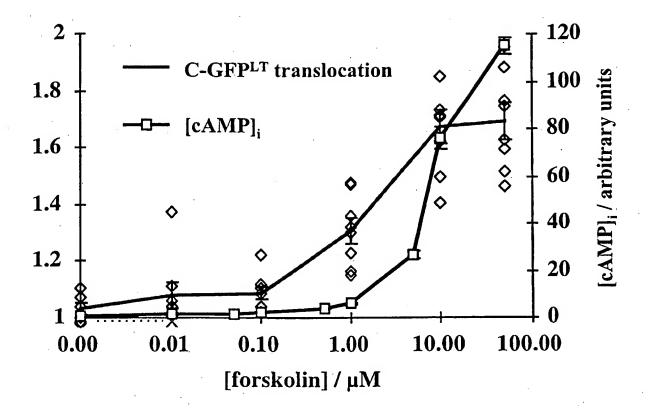
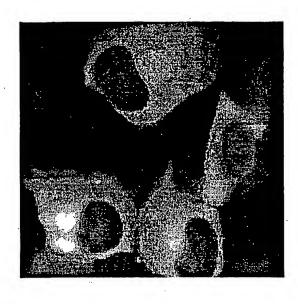
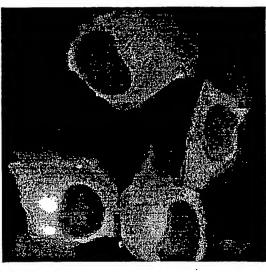


Fig 7



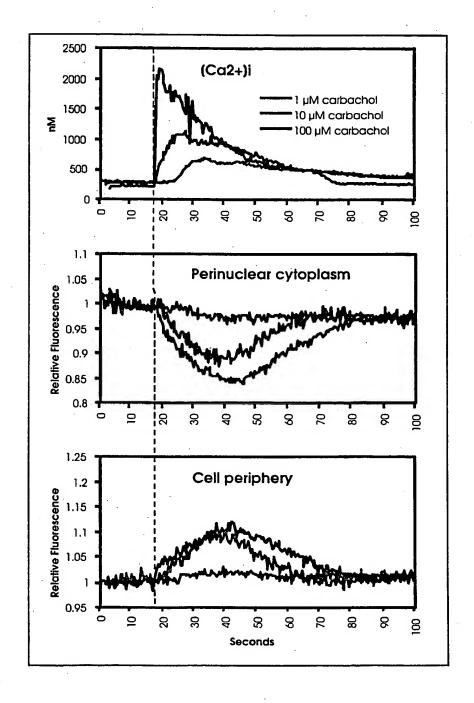
b)

a)

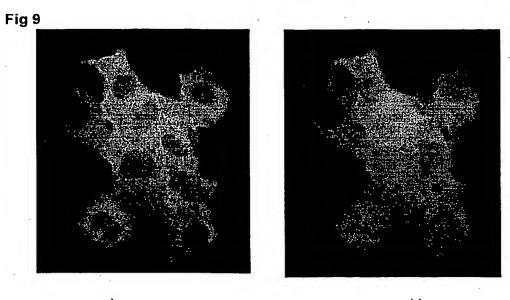


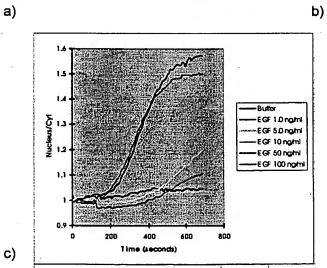
c)

Fig 8









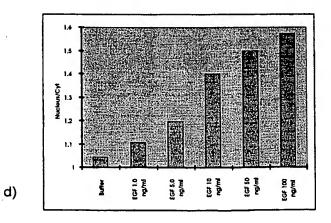
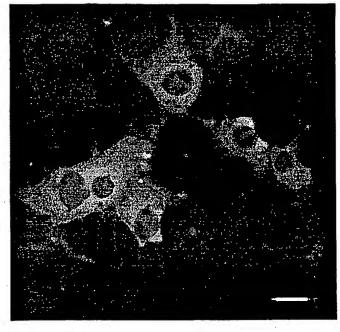
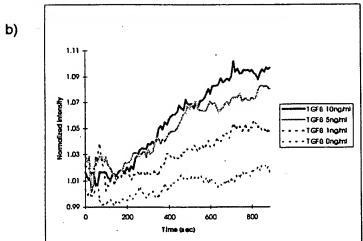


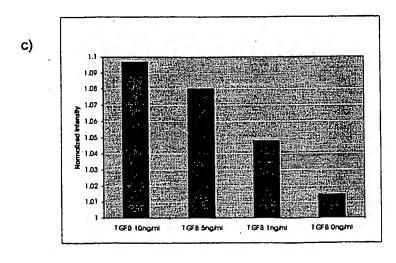


Fig 10



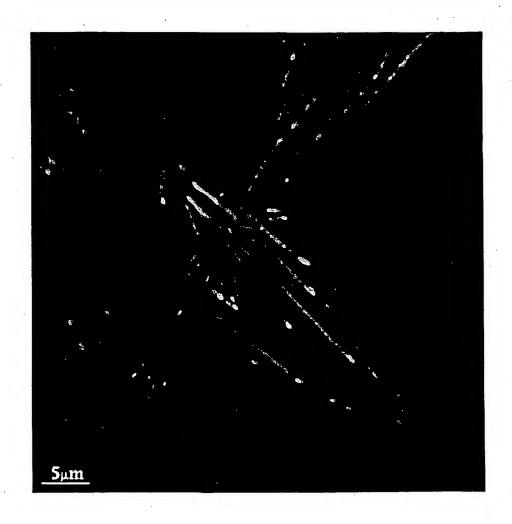






11/12

Fig 11

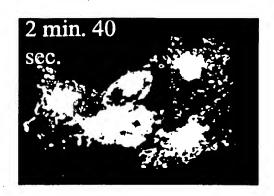


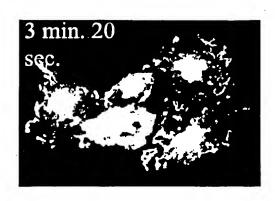
12 / 12

Fig. 12

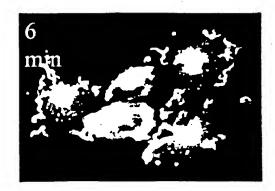












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#### (57) Abstract

Cells are genetically modified to expresss a luminophore, e.g., a modified (F64L, S65T, Y66H) Green Fluorescent Protein (GFP, EGFP) coupled to a component of an intracellular signalling pathway such as a transcription factor, a cGMP- or cAMP-dependent protein kinase, a cyclin-, calmodulin- or phospholipid-dependent or mitogen-activated serine/threonin protein kinase, a tyrosine protein kinase, or a protein phosphatase (e.g. PKA, PKC, Erk, Smad, VASP, actin, p38, Jnk1, PKG, IkappaB, CDK2, Grk5, Zap70, p85, protein-tyrosine phosphatase 1C, Stat5, NFAT, NFkappaB, RhoA, PKB). An influence modulates the intracellular signalling pathway in such a way that the luminophore is being redistributed or translocated with the component in living cells in a manner experimentally determined to be correlated to the degree of the influence. Measurement of redistribution is performed by recording of light intensity, fluorescence lifetime, polarization, wavelength shift, resonance energy transfer, or other properties by an apparatus consisting of e.g. a fluorescence microscope and a CCD camera. Data stored as digital images are processed to numbers representing the degree of redistribution. The method can be used as a screening program for identifying a compound that modulates a component and is capable of treating a disease related to the function of the component.

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Category *	Citation of document, with indication, where appropriate, or the relevant passages	Theodor to diam to
X	WO 95 07463 A (UNIV COLUMBIA ;WOODS HOLE OCEANOGRAPHIC INST (US); CHALFIE MARTIN) 16 March 1995 cited in the application	1-27, 30-40, 42-60, 64-84,
	see claim 26	87,88
Y	see the whole document	28,29, 41,61-63
Y	WO 96 23898 A (NOVONORDISK AS ;THASTRUP OLE (DK); TULLIN SOEREN (DK); POULSEN LAR) 8 August 1996	28,29, 41,61-63
X	see the whole document see page 8-17	42,43, 46,47
X	WO 96 03649 A (UNIV NORTH CAROLINA) 8 February 1996 see page 49; example 6.10	45
Ρ,Χ	WO 97 20931 A (US HEALTH ; HTUN HAN (US); HAGER GORDON L (US)) 12 June 1997 see claims 41-58	40,44
Ρ,Χ	WO 97 30074 A (CYTOGEN CORP ;UNIV NORTH CAROLINA (US)) 21 August 1997 see page 57	44
P , X	WO 98 02571 A (TSIEN ROGER Y ;CUBITT ANDREW B (US); UNIV CALIFORNIA (US)) 22 January 1998	1-27, 30-40, 42-50, 52-54, 57-60, 64-82,88
	see claims	
Ε.	WO 98 30715 A (ISACOFF EHUD Y ;SIEGAL MICAH S (US); UNIV CALIFORNIA (US); CALIFOR) 16 July 1998 see the whole document	1-84,87, 88
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	cited in the application see abstract	
X	SCHMIDT, D.J. ET AL.: "Dynamic analysis of alpha-PKC-GFP chimera translocation events in smooth muscle with ultra-high speed 3D fluorescence microscopy" FASEB JOURNAL,	1-43,46, 47,49, 53-57, 59-82,88
	vol. 11, no. 3, 28 February 1997, page A505 XP002077257 cited in the application see abstract	
X	GERISCH, GUENTHER ET AL: "Chemoattractant-controlled accumulation of coronin at the leading edge of Dictyostelium cells monitored using a green fluorescent protein-coronin fusion protein"  CURR. BIOL. (1995), 5(11), 1280-5 CODEN:  CUBLE2;ISSN: 0960-9822, XP002089510 see abstract p 1281, right col, second full , last sentence	1,40,43, 45
X	SIDOROVA, JULIA M. ET AL: "Cell cycle-regulated phosphorylation of Swi6 controls its nuclear localization" MOL. BIOL. CELL (1995), 6(12), 1641-58 CODEN: MBCEEV; ISSN: 1059-1524, XP002089512 see the whole document	40,43,44
X	HAN HTUN ET AL: "VISUALIZATION OF GLUCOCORTICOID RECEPTOR TRANSLOCATION AND INTRANUCLEAR ORGANIZATION IN LIVING CELLS WITH A GREEN FLUORESCENT PROTEIN CHIMERA" PROCEEDINGS OF THE NATIONAL ACADEMY OF SCIENCES OF USA, vol. 93, no. 10, May 1996, pages 4845-4850, XP002029560 see the whole document	1-40,44, 64-72
	-/	

9

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		PC1/DK 98/00145			
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X .	CAREY K L ET AL: "EVIDENCE USING A GREEN FLUORESCENT PROTEIN-GLUCOCORTICOID RECEPTOR CHIMERA THAT THE RAN/TC4 GTPASE MEDIATES AN ESSENTIAL FUNCTION INDEPENDENT OF NUCLEAR PROTEIN IMPORT" THE JOURNAL OF CELL BIOLOGY.	1-40,44, 64-72			
	vol. 133, no. 5, June 1996, pages 985-996, XP000670316 cited in the application see the whole document				
X	OGAWA H ET AL: "LOCALIZATION, TRAFFICKING, AND TEMPERATURE-DEPENDENCE OF THE AEQUOREA GREEN FLUORESCENT PROTEIN IN CULTURES VERTEBRATE CELLS" PROCEEDINGS OF THE NATIONAL ACADEMY OF SCIENCES OF USA, vol. 92, no. 25, 5 December 1995, pages 11899-11903, XP002029556 see the whole document	1-40,44, 64-72			
X	WESTPHAL, MONIKA ET AL: "Microfilament dynamics during cell movement and chemotaxis monitored using a GFP - actin fusion protein" CURR. BIOL. (1997), 7(3), 176-183 CODEN: CUBLE2;ISSN: 0960-9822, XP002090291 see page 181, left-hand column, line 1	1,40,43, 45			
X	TODA, TAKASHI ET AL: "The fission yeast sts5+ gene is required for maintenance of growth polarity and functionally interacts with protein kinase C and an osmosensing MAP kinase pathway"  J. CELL SCI. (1996), 109(9), 2331-2342  CODEN: JNCSAI;ISSN: 0021-9533, XP002090292 see abstract	40,42			
A	WEBB, CHRIS D. ET AL: "Use of green fluorescent protein for visualization of cell-specific gene expression and subcellular protein localization during sporulation in Bacillus subtilis"  J. BACTERIOL. (1995), 177(20), 5906-11  CODEN: JOBAAY; ISSN: 0021-9193, XP002089513 see the whole document	44			
A	WO 94 23039 A (CANCER RES INST ROYAL; MARSHALL CHRISTOPHER JOHN (GB); ASHWORTH AL) 13 October 1994 see the whole document	1-84,87, 88			

ational application No. PCT/DK 98/00145

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)
This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:
1. X Claims Nos.: because they relate to subject matter not required to be searched by this Authority, namely:
Although claims 83-84 and claim 87 relate to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition (Rule 39.1(iv) PCT - Method for treatment of the human or animal body by therapy).  2. X Claims Nos.:  85,86  because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:
see FURTHER INFORMATION sheet PCT/ISA/210
Claims Nos.:     because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).
Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)
This International Searching Authority found multiple inventions in this international application, as follows:
see additional sheet
1. As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.
As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:
4. No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:
Remark on Protest  X The additional search fees were accompanied by the applicant's protest.
No protest accompanied the payment of additional search fees.

## FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Claims Nos.: 85,86

The subject-matter (compounds per se) is solely characterised in claims 85 and 86 by the result to be achieved, no support of a technical character is derivable from the description for the technical formulation of the subject of the search, accordingly no scope of a search could be defined and a meaningfull search is hence not possible.

#### FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

This International Searching Authority found multiple (groups of) inventions in this international application, as follows:

1. Claims: Partially: 1-43, 46, 59-82 and 88; Entirely: 47, 49, 53-57

Methods for extracting information from influences on a living cell involving observing spatial redistribution or modulation of a luminophore linked to a biologically active molecule, in particular to a molecule involved in intracellular signalling pathways, nucleic acids encoding fusion proteins comprising bothe the luminophore and the biological active molecule, cells containing and expressing these nucleic acids, as well as methods and apparatuses involving above products, inso far as related to the biologically active protein being serine/threonine protein kinases

2. Claims: Partially: 1-41, 43, 59-82 and 88; Entirely: 48

Methods for extracting information from influences on a living cell involving observing spatial redistribution or modulation of a luminophore linked to a biologically active molecule, in particular to a molecule involved in intracellular signalling pathways, nucleic acids encoding fusion proteins comprising bothe the luminophore and the biological active molecule, cells containing and expressing these nucleic acids, as well as methods and apparatuses involving above products, inso far as related to the biologically active protein being to tyrosine kinases

3. Claims: Partially: 1-43, 46, 59-82 and 88; Entirely: 50, 51

MMethods for extracting information from influences on a living cell involving observing spatial redistribution or modulation of a luminophore linked to a biologically active molecule, in particular to a molecule involved in intracellular signalling pathways, nucleic acids encoding fusion proteins comprising bothe the luminophore and the biological active molecule, cells containing and expressing these nucleic acids, as well as methods and apparatuses involving above products, inso far as related to the biologically active protein being to cAMP dependent protein kinases.

4. Claims: Partially: 1-43, 46, 59-82 and 88; Entirely: 52

MMethods for extracting information from influences on a living cell involving observing spatial redistribution or modulation of a luminophore linked to a biologically active

## FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

molecule, in particular to a molecule involved in intracellular signalling pathways, nucleic acids encoding fusion proteins comprising bothe the luminophore and the biological active molecule, cells containing and expressing these nucleic acids, as well as methods and apparatuses involving above products, inso far as related to the biologically active protein being cGMP dependent protein kinases

5. Claims: Partially: 1-43, 59-82 and 88; Entirely: 58

Methods for extracting information from influences on a living cell involving observing spatial redistribution or modulation of a luminophore linked to a biologically active molecule, in particular to a molecule involved in intracellular signalling pathways, nucleic acids encoding fusion proteins comprising bothe the luminophore and the biological active molecule, cells containing and expressing these nucleic acids, as well as methods and apparatuses involving above products, inso far as related to the biologically active protein being protein phosphatases

6. Claims: Partially: 1-41, 43, 59-82 and 88; Entirely: 44

Methods for extracting information from influences on a living cell involving observing spatial redistribution or modulation of a luminophore linked to a biologically active molecule, in particular to a molecule involved in intracellular signalling pathways, nucleic acids encoding fusion proteins comprising bothe the luminophore and the biological active molecule, cells containing and expressing these nucleic acids, as well as methods and apparatuses involving above products, inso far as related to the biologically active protein being to transcription factors

7. Claims: Partially: 1-41, 43, 59-82 and 88; Entirely: 45

Methods for extracting information from influences on a living cell involving observing spatial redistribution or modulation of a luminophore linked to a biologically active molecule, in particular to a molecule involved in intracellular signalling pathways, nucleic acids encoding fusion proteins comprising bothe the luminophore and the biological active molecule, cells containing and expressing these nucleic acids, as well as methods and apparatuses involving above products, inso far as related to the biologically active protein being to proteins associated with the cytoskeletal network

Information on patent family members

In. Jational Application No PCT/DK 98/00145

Patent document cited in search report		Publication date	Patent family member(s)		Publication date	
WO 9711094	Α	27-03-1997	AU CA EP	4482996 A 2232727 A 0851874 A	09-04-1997 27-03-1997 08-07-1998	
 WO 9101305	A	07-02-1991	AU CA EP JP US	6054590 A 2064766 A 0484369 A 5501862 T 5683888 A	22-02-1991 23-01-1991 13-05-1992 08-04-1993	
 WO 9507463	А	16-03-1995	US AU AU CA EP JP	5491084 A 694745 B 7795794 A 2169298 A 0759170 A 9505981 T	13-02-1996 30-07-1998 27-03-1995 16-03-1995 26-02-1997 17-06-1997	
WO 9623898	Α .	08-08-1996	AU CA EP	4483096 A 2217700 A 0815257 A	21-08-1996 08-08-1996 07-01-1998	
WO 9603649	Α	08-02-1996	AU CA EP JP	3146095 A 2195629 A 0772773 A 10503369 T	22-02-1996 08-02-1996 14-05-1997 31-03-1998	
WO 9720931	A	12-06-1997	AU CA	1283497 A 2239951 A	27-06-1997 12-06-1997	
WO 9730074	Α	21-08-1997	AU	2272397 A	02-09-1997	
WO 9802571	Α	22-01-1998	AU	3801997 A	09-02-1998	
WO 9830715	Α	16-07-1998	AU	5090498 A	03-08-1998	
WO 9423039	А	13-10-1994	AU EP JP AU CA EP WO JP	677834 B 6382394 A 0703984 A 9501302 T 696939 B 1586195 A 2182967 A 0742827 A 9521923 A 9508795 T	08-05-1997 24-10-1994 03-04-1996 10-02-1997 24-09-1998 29-08-1995 17-08-1995 20-11-1996 17-08-1995	